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Urolithiasis: Risk factors, epidemiology, diagnosis and management modalities: a comprehensive review

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ABSTRACT

Urolithiasis is a common worldwide problem. If left untreated it causes infections of urinary tract, permanent renal damage and finally loss of kidney functions. Pakistan is included in the stone belt region. Therefore, the high prevalence of urolithiasis has been reported. Study aims were to review the risk factor, prevalence, diagnostic techniques and management modalities of urolithiasis used in developing and developed countries, so that high prevalence can be prevented by adopting some simple conservative method. In the present review, we searched for data using Science Direct, Elsevier, Springer Link (Springer), Google Scholar and PubMed. The search included the keywords "Renal stones, risk factor, incidence rate, lifestyle, climate condition, diagnosis of urolithiasis, treatment options, the prevalence in Pakistan and worldwide. Urolithiasis has afflicted the human kind since antiquity. The prevalence of renal stones are rising all over the world due to drastic changes in climate, dietary pattern including poor quality diet, high content of minerals in water and low intake of water, delayed or improper diagnosis and treatment. So the data have been compiled from different sources in comprehensive way to describe the urolithiasis from cases to management which might be helpful for the physicians, clinicians and traditional healers to minimize the urolithiasis burden by accurate in time diagnosis and treatment of affected ones.

INTRODUCTION

Urolithiasis is a common health issue worldwide and causes an enormous socio-economic impact (1). Among other countries, it is more prevalent in Pakistan. It is a painful urological disorder. In economically developed countries, the prevalence rate ranged between 4% and 20%. During the 20th century its incidence has been increased considerably. The common type of renal stone contains calcium. It was reported that calcium oxalate (75%-90%) has major contribution in calculi formation, followed by uric acid (5%-20%), calcium phosphate (6%-13%), struvite (2%-15%), apatite (1%) and cystine (0.5%-1%). This may be present in combination with oxalate and phosphate. Approximately 80% of all kidney stones are of calcium oxalate and calcium phosphate type. Dihydrate calcium oxalates are less common as compared to monohydrate variety. Among all types of stones, Phosphate stones comprise only about 7% of all stones while its struvite (magnesium ammonium phosphate) form is uncommon. Majority of the people living in northern areas of Pakistan have oxalates stones whereas those living in rural areas of the south region have phosphate stones. Prevalence of renal stones is increasing worldwide due to multiple factors including changes in lifestyle as well as in the environment. Urolithiasis is the 3rd most common disease worldwide. The most prevalent areas includes Scandinavian countries, Mediterrenanian, British Isles, Australia, and central Europe, some parts of Malaysia, China, Pakistan, and Western India, Sudan, Thailand, Indonesia, Philippines, Saudi Arabia, UAE (2). A vast number of contributing factors include age, gender, dietary habits, fluid intake, climate, occupation and education level, socioeconomic status, racial or national distribution, genetic and metabolic disease were reported in the development of calculi. Dietary and environmental factors play a vital role in the initiation of stone formation (3). Foods which are rich with oxalates should be avoided in patients with hyperoxaluria induced stones. Signs and symptoms of kidney stones include pain, pyrexia, vomiting, nausea, urinary tract infection, abnormal urine color, hematuria, chills, and urethral irritation. If the stone becomes lodged at the ureterovesicular junction, patients will complain of marked urinary urgency and frequency. Pain is localized to the flank, is usually severe, and may be associated with nausea and vomiting (4). Stones may pass spontaneously or they are dissolved. Otherwise, small and multiple stones (metabolic) need to be managed conservatively by specific therapeutic strategies. Calcium stones are also formed in the kidney by the increased absorption of calcium from the intestine or it may be idiopathic. In both these conditions, thiazide diuretics are effective and are used along with other forms of treatment such as restriction of calcium intake in the diet. Administration of acetazolamide along with sodium bicarbonate makes the urine alkaline and helps in the excretion of uric acid and cystine in the urine, because both uric acid and cystine are soluble in alkaline urine. This prevents the deposition of uric acid and cystine in the urine to form their stones (5). Calcium oxalate stones are treated by increasing fluid intake, restricting green leafy vegetables, tomatoes and tea (6). Medicinal plants also have potential role in the management of renal calculi. The exact mechanism of herbal medicines used to treat urolithiasis is not well understood still but it was reported that phytochemical constituents acted as neutraceuticals, immunomodulators, boost body oxidant status or provided antioxidant compounds, prevent crystallization and nucleation of crystals as well as acted as diuretics. These diverse properties of medicinal plants are due to the presence of various phytochemical constituents including Alkaloids, Anthraquinones, Flavonoids, Glycosides, Phenols, Saponins, Steroids, Sterols, Tannins, Terpenoids, Triterpenoids, Phenols, Phytosterols, Hydrocarbons, Mono and sesquiterpenes, Anthraquinone, Phlobatanins and many others. Flowers, Leaves, bark, fruit, seeds and even whole parts of medicinal plants were ingested to treat urolithiasis and these parts or their extracts are consumed orally as sole preparation or might be mixed with different other foods or drinks. The dose of the herbs preparations also depends upon sex, age and current health status of patients (7). Indications of surgical treatment include hydronephrosis, anuria, bladder stones, frequent bouts of severe pain and persistent pain (8). Types of fragmentation include lithotripsy (9) nephrolithotomy (10), pyelolithotomy (11) and ureterolithotomy (12). The objectives of this comprehensive review is to described the risk factors and pathophysiology of urolithiasis, types of stones, epidemiology of urolithiasis, diagnostic and management modalities could be helpful for physicians and traditional healers.

Statistical Analysis Statement

Appropriate clinical and epidemiological studies were statistically examined where appropriate to reinforce the

review. Retrospective and cross-sectional studies that completed peer review were used for determining the prevalence and incidence rates. A comparative study is being carried out in order to demonstrate the variations in risk profiles between the populations of developed and developing nations. Major risk factors including hydration levels, eating habits, and weather conditions have been demonstrated using descriptive statistics, such as mean percentages and frequency distributions, that were cited from the body of existing literature. To evaluate the significance of the results, p-values and intervals of trust were examined when available. An evidence-based understanding of the burden and treatment of urolithiasis is aided by this methodology.

RISK FACTORS OF UROLITHIASIS AND PATHOPHYSIOLOGY

Risk factors associated with the development of renal calculi can be grouped into intrinsic or extrinsic factors. The intrinsic factors include gender, age, family history and ethnicity while the extrinsic factors include dietary habits and lifestyle, environmental and climate change, educational level and occupation. Dietary habits and climate are the principal factors contributing to the incidence, prevalence, constituent and recurrence of calculi. Some other risk factors which also contribute to the formation of renal calculi are metabolic disorders including hypertension and diabetes mellitus in patients with urinary tract infection or renal tubular acidosis (13).

The incidence of renal stone formation is increased with increasing age reaching to the peak level in the age group 30-60 years of age and starts declining in elderly people aged more than 60 years. The increased incidence of renal stones in middle aged population is due to their laborious work which they do most commonly at the age under 30-60 years than other people below or over this age (14). Subsequently, the increased rate of dehydration as a result of the lower water intake and excessive sweating during heavy work in hot and dry climate also contribute to the development of renal stones in these populations. Additionally, occupational stress and unhealthy lifestyle (staying up for a longer time or irregular and imbalanced diet) in these people led to the formation of urinary calculi (13, 15, 16).

Worldwide, men are more prone to urolithiasis than women who may be associated with variation in dietary habits. Men are more likely to drink coffee and alcohol in excessive amount than in women and men also consumed rich protein diet such as meat. Estrogen in women appears to inhibit the stone formation which regulates the 1,25-dihydroxy-vitamin D synthesis while testosterone in men can promote the formation of renal stones (14). Rather, anatomical differences can also play a significant role in stone formation as men are more likely to suffer from benign hyperplasia of the prostate leading to urethral obstruction resulting in stone formation (17).

Dietary habits and lifestyle also play a significant role in the formation of renal calculi. Most of the people in developing countries fed on vegetables and cereals which contains an increased concentration of oxalate and its precursors. Additionally, western diet contains excess protein, fats, calcium and sodium contributing to the development of renal calculi resulting in higher incidence of urolithiasis in many Asian countries including India, China, Japan and Pakistan (18). Excessive meat consumption can also form the uric acid stones resulting in hyperuricemia (19).

One of the risk factors for urolithiasis is the less intake of water leading to dehydration and renal stone formation as described in figure 1 with pathophysiology of stone development and the possible targets of therapeutic drugs. In Pakistan, India and Sri Lanka, underground water is the main source of drinking water which due to evaporation is undergoing mineralization. High mineral contents like fluoride, calcium, sodium, phosphates and magnesium in drinking water are reported to be coupled with the formation of calcium oxalate stones (20). Urolithiasis prevalence in people using high fluorine water for drinking is 4.6 times higher than those residing in the fluorine free area (21). People working in offices with inadequate physical activity are more prone to urolithiasis compared to those doing laborious work in the field (22).

There is a strong correlation between geographical factors and climatic changes with urolithiasis. Hot dry climate results in higher sweating leading to higher evaporation of water from the body through the skin resulting in concentrated urine which as a risk factor contributes to the precipitation of crystals and formation of stones in renal system. During the summer and autumn season, the incidence and prevalence of urolithiasis are higher than in winter and spring in many regions of the world like Pakistan, India, Iran and Saudi Arabia

(13, 16, 23, 24).
Genetic factors also contribute to urolithiasis. Mutations in SLC3A1, SLC7A9 gene can cause cystine stone (25). Additionally, patients with uric acid stones have been reported having a mutation in SLC22A12 and SLC2A9 gene. Certain enzyme deficiencies also contribute to renal stone formation such as alanine glyoxylate aminotransferase (AGT), 4-hydroxy-2-oxoglutarate aldolase (HOGA1) or glyoxylate reductase/ hydroxypyruvate reductase (GRHPR) deficiency may result in the formation of most common renal calculi, calcium oxalate stones. Many epidemiological studies conducted in Asian countries since the 1960s, reported that people with a family history of renal calculi are more likely to develop urolithiasis than those without a family history of renal stones (16, 18).

TYPES OF CALCULI AND THEIR ANATOMICAL LOCATIONS

It was reported that the urolithiasis prevalence and incidence had been significantly increased with prominent decrease in vesicle calculi proportion. Lower urinary tract (LUT) stones were the major site for calculi formation about thirty to seventy years ago and accounted for 30% to 94% in different countries including Pakistan, Japan, Malaysia, China, India and Thailand. But now due to development in economy trend has been changed progressively to upper urinary tract (UUT) stones formation which now comprised about 85% to 93% of the major part of urolithiasis (18, 20, 26-28).
In Asian countries different types of calculi have been diagnosed on the basis of chemical composition of stone analysis which included as calcium oxalate, uric acid, calcium phosphate, struvite, apatite and cystine from 75% to 90%, 5% to 20%, 6% to 13%), 2% to 15%, 1% and 0.5% to 1%, respectively (20, 29, 30). It was reported in various countries like Indonesia, China, India and Japan that the ratio of calcium oxalate and uric acid stones is potentially increasing since 1960s (31, 32) while on the other hand struvite stone composed of magnesium ammonium phosphate and associated with UTI are decreasing in different countries including Iran, India and Japan. Moreover, a vast difference in developed and developing countries has been reported. In developed countries calcium oxalate (90% vs. 75%) and uric acid calculi (15% vs. 5%) were found as more common while struvite stones (7% vs. 14%) in developing countries (33). Further, Ansari et al (2005) investigated that calcium oxalate as the commonest component of staghorn stones that was in contrast to the previous knowledge that magnesium ammonium phosphate was the major component (34) . It is also reported that the composition as varies with the variation in anatomical locations of stone and found that calcium oxalate (75%) and hydroxyapatite (51%) are the common constituents of UUT calculi in Pakistan and in LUT the ammonium acid urate and calcium oxalate combinations , especially in children, are more frequent calculi types (Figure 2).
Ahmad et al (2015) has observed about 5371 patients and reported that the distribution of calculi in different parts of the urinary tract significantly varied. It was reported that calculi distributed as Renal (73.3%), Pelviureteric junction (PUJ) (2.3%), ureter (13%) as proximal, middle and distal thirds, Vesico-uretic junction (VUJ) (9.8%), Vesical (1.1%) and urethral (0.5%). In addition, it was noted that the size of calculi also significantly varies at different anatomical position such in renal area it ranges from 0.4–6 cm, in PUJ from 11–19 mm, in ureter from 4–16 mm, in VUJ from 5–18 mm while in vesical and urether range from 5–25 mm and 8–10 mm, respectively (Figure 2) (35).

EPIDEMIOLOGY OF UROLITHIASIS

Urolithiasis and Pakistan

Historical studies indicate that the highest prevalence of urolithiasis in the sub-continent was in Sindh (36). A study from Sindh Institute of Urology and Transplantation (SIUT), Karachi shows that 50-60% of the urological cases were of urolithiasis. Similarly, in another institute, 159 patients were suffering from urolithiasis 56% were of bladder calculi that went for open surgery (37). Another study showed that 46.6% of the children were suffering from bladder calculi (38). It has been observed that the occurrence of endemic bladder calculi in children still exists in rural areas of Sindh and poor localities of urban cities (39).
A study showed that the peak age of observing urolithiasis was in 30's and 40's year of age with a male to female ratio of 3:1 (40). It may be due to the reason that women produce more estrogen hormone which can produce a large amount of citric acid that prevents the stone formation. The occurrence was more common in extremely

hot climate areas which could be attributed to being a major reason behind the stone disease. More patients' visits to clinics were observed in the summer season with a complaint of renal calculi, calculus anuria, pyelonephritis and chronic renal failure. Among renal stone patients, 20% had a family history. The dietary pattern of the urolithiasis patients lacked protein in 27% cases, low calcium intake in 60%, high oxalate intake in 38%, and high sodium intake in 20% of patients additionally a low water intake is also a predisposing factor (41) One of the major risk factor common in Pakistan is hypocitraturia; patients should be encouraged to take citrus fruits like oranges and lemon which increase the urine and citric acid level of the urine and hence is useful in preventing the calcium oxalate stones formation (42). A study was conducted in the Pakistani population of Karachi, to determine the prevalence of urolithiasis. They found silent kidney stones in 3% of cases. All stone sufferers were males. The left kidney was most affected. They concluded that usual figures of incidence and prevalence of stone disease drawn from current patient data, there is a prevalence of 3% silent stones that may be discovered incidentally or by screening (43)

The family history of stone diseases is found in 16% of cases with 4% in the maternal side and 12% from the paternal side. The serum phosphate level was higher in stone carrier patients (20). In spite of advancement in the management of kidney stone, the prevalence of nephrolithiasis is increasing in Pakistan. In Pakistan, the frequency of renal failure is 8% due to renal stones. Similarly, renal and ureteral calculi cause 5.3% acute renal failure(44). Prevalence of life threatening complication is 12% due to renal stones (45). Prevalence of kidney stones is 15% in Pakistan and Turkey (43). The annual incidence of end stage renal failure is 100 new cases per million populations (46). The prevalence of bladder stones is decreasing in most of the countries. The incidence of calculus disease was 60% in the lower tract in 1980 that changed to 15% in 1990 (47). Mortazavi and Mahbubi (2007) had investigated risk factors and clinical features of urolithiasis in children. TTotal patients with urolithiasis were 184 including 84 males and 100 females. Age of children was between 2 months and 14 years. The diameter of the stone was 3-27 mm. Gross hematuria, restlessness and urinary tract infection were the main manifestations of urolithiasis. Urinary tract infection was reported in 40.8% of cases and 41% of cases had a positive family history of urolithiasis. Sterile pyuria was detected in 18.5% cases and anatomic abnormalities were reported in 41% cases. The metabolic evaluation was carried in 162 cases in which 104 (64%) patients had metabolic risk factors including hyperoxaluria (4.3%), cystinuria (7.4%), hyperuricosuria (10.5%) and normocalcemic hypercalciuria (42%) (48).

Worldwide prevalence of Urolithiasis

Prevalence of nephrolithiasis varies in different countries of the World; 20% in Saudi Arabia, 13% in North America, 5-9% in Europe and 1% in Asia. The prevalence and incidence of urolithiasis have increased in most of the countries of Asia over the last several decades. Apart from climate, dietary habits and genetic factors, the increasing usage and improvements in the sensitivity of high-tech imaging examination technology (computed tomography or ultrasonography) can also account for it. There is no evident difference in recurrence rate of urolithiasis among Asian countries, which is about 6-17% after 1 year, 21-53% after 35 years, and the lifetime risk of recurrence is estimated to be 60-80%. In various Asian and European countries prevalence rate was documented as China prevalence of renal stone was 6.4%, South Korea 2008-2013 rate of prevalence was 12.2 to 9.2%, Japan 1965-1995 Urolithiasis rate was 4.3 to 9.0%, Russia 1980-2008 Urolithiasis was 2-3%, India 2013 Kidney stones 7.6%, Pakistan 1975-2010 Urolithiasis 16%, Iraq 2005 Urolithiasis was 1%, Turkey 2008 Urolithiasis was 11%. The prevalence of renal stones is more in male than female. White Caucasians are more affected by kidney stones than Blacks (49). Daudon, (2005) stated that the prevalence of nephrolithiasis is 10% in France. Most prevalent kidney stones in France are calcium oxalate stones and are mostly associated with diabetes mellitus and with high body mass index. Struvite stones are significantly reduced by timely treatment of urinary tract infections caused by urea-splitting bacteria. Urate stones are more common in obese and diabetic people. Other risk factors for kidney stones in France were potassium rich vegetables, insufficient dietary intake of fruits and higher consumption of protein. (50). Stamatelou et al (2003) stated that the prevalence of urolithiasis is 10 to 15% in adult patients. Smith et al (1972) reported that the prevalence of kidney stones in children is 2-3% (51). The study indicates that the prevalence of kidney stones in children is growing (52). There is a link between urolithiasis and childhood obesity and 30% of kidney stones are found in children

having weight more than 90% percentile for age (53). Prevalence of calcium oxalate, calcium phosphate, struvite, cystine and uric acid stones in United States is 40% to 65%, 14% to 30%, 10% to 20%, 5% to 10% and 1% to 4% respectively (54). Agarwal et al., (2000) reported that the prime cause of renal failure is chronic glomerulonephritis and diabetic nephropathy (55). In Western countries, metabolic causes, infection and anatomic abnormalities are found in 90% of cases (56). Stamatiou et al. (2006) conducted a study to investigate the prevalence of urolithiasis in Thebes (57). Prevalence of urolithiasis was reported 15% in People living in Thebes. The overall prevalence of urolithiasis was more in men than in women but the difference in sex and age was not significant. The incidence of vesical calculus is more in Indonesia, Indochina, China, India, Iran, and Turkey. Vesical stones were frequent in Europe in the last 100 years but there was a gradual decrease in the incidence of vesical stones in Europe and prevalence of reno-ureteral calculosis is increasing in Europe. This situation can be related to changing social status and subsequently changes in lifestyles and eating habits. In this way, the prevalence of calcium phosphate and calcium oxalate stones is 70% of all renal stones in economically developed countries such as Japan, Australia, North America, and Europe (Table 1).

DIAGNOSTIC TECHNIQUES FOR UROLITHIASIS

Diagnosis of the urolithiasis is essential for its management and the investigation of patients' family history, lifestyle and medical history play significant role in the diagnosis. For the investigation of predisposing risk factors of urolithiasis medical history is the major component of diagnosis which might reveal the condition of the suffering patients from any disease under different therapies or using medication caused the urolithiasis. Moreover, dietary behavior and family history of affected one's further unveil the potential linkage of stone formation (58). Although, intolerable flank pain and presence of blood in urine are the typical diagnostic features of urolithiasis but still a series of diagnostic investigations are needed as mentioned below.

Urine analysis

The most easy and affordable test to explore the presence of stone in urinary tract is the complete urine examination usually the first morning urine sample. The urine analysis included the tests to find blood in urine, to determine urine volume, pH, sodium, calcium, uric acid, phosphate, creatinine, oxalate, citric acid, cysteine level and any drug crystals (59, 60). The macroscopic examination by naked eye and by dipstick and microscopic examination for the presence of different types of stones are vital component in the diagnosis of urolithiasis. The presence of pus, hematuria, proteins and bacteria are some important findings in urine analysis (61, 62). The pH of urine is the most important indicator for different types of stones like acidic pH favored the formation of uric acid, calcium oxalate, and cysteine crystals while struvite and calcium phosphate crystals formation take place in the alkaline pH (61, 63, 64). Further, urine culture and sensitivity test is also proceeded to rule out the urinary tract infection (60). Moreover, the level of different substances in urine viz. calcium, phosphate urea, creatinine, cysteine, uric acid, citric acid, oxalate and magnesium plays important role in the evaluation of the causal metabolic disorders and risk factors for urolithiasis development (65).

Blood analysis

To investigate the kidneys performance in a patient blood level of urea, creatinine, electrolytes, uric acid, calcium, phosphate, proteins, magnesium and bicarbonate are some important parameters which might fluctuate in metabolic abnormalities (64, 66). In urolithiasis the blood level of urea, creatinine and uric acid are potentially increased which reflect the affected glomerular filtration rate and kidney damage (67). In patients it is necessary to evaluate the parathyroid hormone level if serum calcium level is high (58). Along with minerals, biochemical and hormonal analysis of blood it is helpful to investigate the hematological parameters especially white blood cells count to rule out renal infection (64).

Stone analysis

Various techniques like X-ray crystallography and infrared spectroscopy, are used for the determination of stone composition, which have crucial role in the investigation of the associated metabolic disorders and the nature of substances involved in the stone formation, and thus helps in proper medical intervention. The analysis of stone is used to examine 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 (68)

Radiological Analysis

The final confirmation of stone is made by radio imaging techniques after physical examination, family history and other laboratory investigations. Radiological examinations are very important investigations to provide crucial information about the type and treatment of stones (69). Following are the most important radiological techniques used to confirm the size, shape, anatomical location, number of calculi and even composition of calculi.

Kidney-Ureter-Bladder (KUB) Radiography

In this imaging analysis plain X-rays are used to scan the abdomen which may reveal the locatin, numbers, shape and size of stone in urinary tract. Calcium rich calculi are the common stones detected by this technique as compare to less radiopaque calculi like struvite, uric acid and cysteine. Further, no doubt it is very simple and cost effective method to diagnose urolithiasis but gastrointestinal abnormalities, stool and calcification in extra urinary parts potentially affects the efficacy and utilities of this procedure. Moreover, it continues to be frequently used for preliminary detection but radiation exposures require high level of care both for patients and workers (65, 70).

Ultrasound Radiography

High frequency sound waves are used to in this technique to localize the renal stones. It is very safe and cost effect diagnostic tool with primary choice to diagnose urolithiasis in pregnant female and children. This technique is used as first line radio imaging technique because in this radiation exposure did not create teratogenicity, mutagenicity and carcinogenicity to the fetus (71). Detection of all types of stones except detecting of ureteral calculi is only drawback of this technique (72).

Computed tomography (CT)

Three dimension structures are constructed through the utilization of CT scan in which X-rays beam for imaging are used which rotated around the patient's body to produce series of images. Due to high accuracy, efficiency and speed of non-contrast helical CT with sensitivity and specificity of 96-100% and accuracy of 96-98%, this technique is becoming more popular to find out all types of calculi, their anatomical position, shape, and size of stones without administration of any contrast media. It is on the verge to outweigh all other imaging techniques and has largely replaced IVP (70, 73-75). 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 gynecologic aberrations (65, 76). The use of ionizing radiation is the only major drawback of this urolithiasis diagnostic tool especially in children and pregnant female. Now a days, low-dose unenhanced CT and dual energy CT (DECT) have introduced. 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 (74, 76-78).

Digital Tomosynthesis

This type of imaging technique is used to produce three dimensional image and it was reported that this technique considerably has less radiation exposure associated risks as compared to the widely used noncontrast CT and may come up with more benefits and wider acceptance (79).

Radioisotope Renography or nuclear imaging

In this diagnostic technique radiolabeled with technetium-99 is administered intravenous and emitted radiation are detected by the gamma camera as the radioactive substance travels down the urinary tract providing images of the same (64, 80, 81).

Magnetic resonance imaging

It was commonly used to explore the pathological changes associated with renal stones usually in children and pregnant females. In this technique radiowaves, body's natural magnetic properties and magnets for imaging urinary stones are used and in some cases paramagnetic contrast media is also used to diagnose urolithiasis (76, 80, 82). It is safer than other imaging techniques due to not using ionizing radiations (71, 82), and only risk associated when high doses of paramagnetic contrast are used like teratogenic (76). But it has proved to be a safer alternative with no mandatory requirement for administration of contrast media (71).

Intravenous Pyelography (IVP)

X-rays are used in this technique to scan the renal structure and to find out the urolithiasis after injecting the iodinated contrast media intravenously. After specific intervals a series of X-rays is performed to explore the renal functions, presence of stones with more accurate size, shape and locality in urinary system (80). This technique is more sensitive and specific than KUB and ultrasonography but it's acceptability is controversial due to the use of contrast media associated side effects that range from flushing, nausea, bradycardia to nephrotoxicity and anaphylactic reactions (70). It is contraindicated in patients with impaired renal function, pregnant women, patients on metformin medication and contrast medium allergy (72, 83).

THERAPEUTIC MODALITIES FOR THE MANAGEMENT OF UROLITHIASIS

After the accurate diagnosis of the renal stones, their size, shape, type and location different management modalities are used to remove the stone and associated disorders like drug therapy including allopathic or herbal treatments; stone fragmentation techniques; or surgical removal of the stones. The selection of treatment modality largely depend the size, shape, type, location other pathological conditions as well as on socioeconomic status of patients.

Allopathic Modalities

Allopathic modalities used as medical expulsive therapies (METs) which help in the expulsion of moderate sized calculi present in the urinary tract and in MET calcium channel blockers or alpha-adrenergic blockers with or without corticosteroids are used. In this modality blockage of α-receptors and calcium influx occurred which inhibited the ureteral smooth muscle contractions and enhanced the hydrostatic pressure to facilitate the outward expulsion of the stones along with providing symptomatic relief from renal colic as well. Among various MET drugs like tamsulosin, terazosin and doxazosin, tamsulosin due to well tolerability is most commonly used along with corticosteroid which act as antioedema agents and also aid in alleviating renal colic (73, 84-87) and de la Rosette, 2008, (88, 89).

Allopathic modalities act as diuretics like thiazide, allopurinol and potassium citrate which are used to manage urolithiasis by increasing the production of urine. These agents are usually indicated for the treatment of idiopathic hypercalciuria. Thiazides increased the reabsorption of calcium from proximal and distal convoluted tubules to create hypocalciuric action. The major issue associated with these agents is to produce hypokalemia which can ultimately lead to hypocitraturia, a factor responsible for augmenting urolithiasis, which could be corrected by potassium citrate or amiloride supplementation. Moreover, hypokalemia due to potassium-sparing diuretic could be restored by triamterene but triamterene as drug crystal could be synthesized in users (90-92). Allopurinol acts as a xanthine oxidase inhibitor which is recommended for the treatment of calcium oxalate and uric acid calculi. The biosynthesis of uric acid is decreased from the hypoxanthine and xanthine due to the inhibition of xanthine oxidase thus the urine level of urate is also reduced, which again turns out to be inhibitory for nucleation of calcium oxalate (93, 94) Another xanthine oxidase inhibitor Febuxostat has high potential as compare to allopurinol in reducing urinary level of urate is routinely recommended now a day (95). The urinary citrate level is increased on ingestion of potassium citrate and ultimately soluble citrate calcium complexes are increased which prevent the calcium phosphate and calcium oxalate stone formation in urinary tract. In addition, uric acid stone formation is also prevented with using potassium citrate due to its alkalinizing effect on urine (96, 97). Although, potassium citrate is more efficacious than sodium citrate and sodium bicarbonate but some gastrointestinal abnormalities were reported in patients using these drugs (97, 98). Potassium citrate, allopurinol and thiazide diuretics are known to reduce stone recurrence rates as well (99).

Allopathic drugs which reduce the intestinal absorption of calcium viz sodium cellulose phosphate and ultimately regulate the elevated level of calcium in urine to prevent the calcium calculi formation. It was reported that this agent is very effective to prevent calcium stone prevention but hyperoxaluria and hypomagnesaemia associated stones are some adverse effect of this drug. Further, sodium cellulose phosphate also stimulates the parathyroid hormone secretion to regulate the blood calcium level (100).

One of the other type of allopathic modalities is the chemolytic dissolution therapy which involved the alteration of urinary pH, rearrangement of disulphide and chelation of stone producing salts (101) and this dissolution therapy might be used as systematic like oral or intravenous or use as direct (irrigative) (102). For the treatment

of uric acid crystals potassium citrate or sodium bicarbonate as systemic chemolysis are administered which raise pH of urine (101). Acetazolamide could also be used to induce immediate alkalization which acts as the inhibitor of carbonic anhydrase. This agent is associated with calcium phosphate stones formation so its applications are limited (103). For the dissolution of struvite stones acetohydroxamic acid is administered orally which decrease the bacterial production of ammonia from urea on inhibiting the urease enzyme and ultimately the formation of struvite stones is decreased (104) but the most common drawback of this agent is to cause hemolytic anemia (101). D-penicillamine or α-mercaptopropionylglycine is used for the dissolution of cystine stones by chelation. Urinary chemolytic fluids are used as direct dissolution therapy when systematic dissolution did not work in which irrigation of the urinary system with chemolytic fluids by means of nephrostomy catheters (percutaneous nephrostomy) or ureteric catheters are done and the time period for this therapy ranges from days to weeks. Renacidin, Hemiacidrin and Tham-E (tris[hydroxymethyl] aminomethane) are the fluids which are commonly used to dissolve the stones. Renacidin as multielectrolyte fluid have ability to chelate and dissolution of struvite, calcium and phosphate stones. On the other hand Tham-E has ability to dissolute the cystine stones (98, 102, 105). Chemolytic dissolution therapy can be used as an adjunct to ESWL and PCNL, or it can also be used to avoid surgical procedure (106). Some of the allopathic drugs used to treat urolithiasis are listed in Table 2.

In addition to treat the stones formation, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are the agents used to reduce the urolithiasis associated pain. It was reported that both drugs classes have vital role in pain relieving but NSAIDs cause potential gastrointestinal and renal side effects while opioid analgesics due to causing nausea and vomiting along with urinary retention, respiratory depression and constipation, require administration of antiemetic agents (107-109).

Dietary and medicinal Plants

Apart from allopathic and synthetic formulations medicinal plants and their extracts played vital role in the management of urolithiasis due to their better tolerability, easily availability, low cost and multiple targets of actions. Moreover, it is well reported that phytoconstituents are very efficacious in the prevention of reoccurrence of kidney stones and are safer as compared to synthetic drugs (110). A number of studies revealed that herbal preparations are utilized as therapeutic modality for the treatment of urolithiasis and other ailments of urinary tract some of which were validated scientifically while other are yet required scientific evaluations (111). Their therapeutic affect as renoprotective as well as antiurolithiatic was globally reported. A wide range acceptance of phytotherapy over allopathic therapy is also due to versatile mechanisms of medicinal plants to prevent as well as to treat the renal stones while on the other hand allopathic medicines have ability to handle urolithiasis only on single aspect at a time of stone pathophysiology (Figures 1). Some of the common ways by which dietary and medicinal plants prevent and treat the urolithiasis are acting as a diuretic, lower the urinary oxalate and calcium excretion as well as enhance the excretion of citrate in urine, alkalization, antioxidants, antimicrobial, anti-inflammatory, nephroprotective, cytoprotective and antispasmodic effects. Glycosaminoglycans (GAGs) a common phytochemical has potential to prevent the crystallization of the calcium oxalate stones. In addition many phytochemicals have potential to inhibit the crystal nucleation, growth as well as aggregation in a manner similar to that of natural urinary inhibitors (100, 112). Grape fruit and lemon juice were evaluated *in vivo* and *in vitro* studies have ability to reduce the calcium oxalate crystallization by converting into calcium citrate which are more soluble and easily excreted in urine (113, 114).

Although, the exact mechanism of phytotherapeutic molecules is not well understood but it was evaluated both through *in vivo* as well as *in vitro* studies that a number of therapeutic herbs and their components have potential to prevent and to treat urolithiasis. Many anti-urolithiatics plants have antioxidant potential and it is considered that this property of various herbal medicines might be involve in the prevention of stone formation by inhibiting nucleation, aggregation and growth of calcium oxalate crystals. It was reported that about more than 8,000 phytoconstituents present in various vegetables and fruits that induce the most abundant dietary antioxidants (115), and these phytochemicals showed significant potential against renal damaging oxidative stress. The most important antioxidants present in grape seeds and green tea includes epicatechin and catechin (116) have metal chelating and radical scavenging activities or genetic modulation effects for some enzymes and

proteins (117), and these properties provides protective characteristics against stone formation, against kidney failure and kidney damage associated with oxidative stress (118, 119).
In NRK-52E renal proximal tubular cell line treated with calcium oxalate monohydrate (COM), catechines as antioxidant enhanced the activity of SOD which reestablished the caspase 3 and mitochondrial membrane proteolysis potential (120) and it was reported that increased SOD activity of catechins halted the calcification of the renal papilla and COM content of papillary calculi (93, 118-120). It was also reported that 8-Hydroxy-20-deoxyguanosine (8-OHdG), Osteopontin (OPN) and Malondialdehyde (MDA) activities in ethylene glycol induced rat model of nephrolithiasis were also regulated by catechines (120). Moreover, epigallocatechin-3-gallate (EGCG) an essential catechine, prevent the attachment of COM with Madin–Darby canine kidney (MDCK) cells by reducing the expression of α-enolase protein and ultimately prevent the COM aggregation (121)(122). Further, it was reported in rats model that catechine prevent calcium oxalate stone formation by restoring the diameter of the capillaries and vessels in the cortex, by inhibiting the glomeruli and tubules degeneration, and by decreasing the hyper permeability of the capillary (123). Diosmin a flavonoid glycoside present in wide range of vegetable and fruits have antiurolithiatic potential and it was reported that due to its antioxidant activity it prevent the kidneys due to oxidative stress, nephro-toxicity and diabetic associated kidney damage (124). Researches revealed that nephroprotective activity of diosmin is its modulatory effect on Bax and p53 proteins expression, increased the production of antioxidant enzymes and inhibit lipid peroxidation (125). Moreover, diosmin also lowered the pH of urine which low the proteins excretion in urine, enhanced the urine potassium and magnesium concentration with diuretic activity (126). In addition to catechine and diosmin antioxidant phytoconstituents a large number of molecules responsible for antioxidant and antirolithiasic activities are present in dietary as well as in herbal plants including rutin, quercetin, and hyperoside (127). These phytoconstituents also prevent the stone formation by modulating the glomerulus filtration and prevent the growth and aggregation renal calculi (128). This preventive action of medicinal plants might be due to their anti-inflammatory activity along with the antioxidant activities. Such encouraging diuretic, anti-inflamatory, antioxidant and hypo-uricemic effects of medicinal plants have made them more popular than allopathic drugs (129) .

Surgical Modalities

Surgical modalities are the interventions used to remove the renal stones which are larger in size or are very proximal in location or possess staghorn contours and when such stones did not give recovering response to medicinal modalities (130).

Extracorporeal shock wave lithotripsy (ESWL)

Extracorporeal shock wave lithotripsy is very popular fragmentation modality used to remove renal stones usually having size less than 2cm. In this procedure a lithotripter is used to generate the shock waves and strikes onto fluoroscopy guided renal stones to generate small fragments 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. Urine acts as drainage media for the fragmented stone from the body. Electrohydraulic, electromagnetic, or piezoelectric are the sources one of which could be utilized as source of energy in a lithotripter for generating shock waves (72). The technique has ability to remove the stones present in renal pelvic and calyx of different types including struvite stones, ureteric stones and staghorn stones (130). The important factor for its acceptability is that not any type of anesthesia is required and on outpatients could be performed safely (131). Stones residual, hemorrhage, renal tissue injury and stone recurrence are some associated ESWL complications (72, 100). Now a day's third generation electromagnetic shock wave lithotripter has been introduced with different trade names to regulate these adverse effects (132).

Ureteroscopy

Ureteroscopy another technique used to remove the renal stone by fragmentation and extraction. In this technique a small telescope also known as ureteroscope passes through the urethra upto 2/3 ureter via bladder ((133-135) and ballistic and laser (holmium: yttrium-aluminium-garnet laser/holmium: YAG laser) lithotripsy are used to treat urolithiasis especially in children and (64, 134) in pregnant women and in patients after urinary diversion (136, 137). Although, a wide advancement has been made in this procedure but still hematuria, urinary

system infection, steinstrasse, ureteral injury and perforation are the most important ureteroscopy associated complications (70).

Laparoscopic surgery

Laparoscopic surgery is a surgical modality in which 3 to 4 incisions are made through which hollow tubes are inserted by which surgical instruments are passes to perform the surgery. In some cases nephroscope to visualize as well as to remove the stone is also passes through one of the tube. This technique is not usually performed in routine but used to treat the cases in which minimally invasive techniques failed to treat urolithiasis Laparascopic surgery, although less frequently performed now, is indicated in cases and where urolithiasis is associated with renal abnormality or other complications (64, 138, 139).

Percutaneous nephrolithotomy (PCNL)

PCNL is a urolithiasis management modality with minimum invasive procedure to remove the renal stones by fragmentation and extraction. In this fragmentation technique a small incision is made on the back of the patient for the insertion of nephroscope to break the stones present in the kidney pyelocalyceal system and proximal ureters (140-143). For the removal of multiple stones with size more than 2cm in diameter from renal pelvis or calyx this procedure is consider as efficient (Purpurowicz, 2010). Damage to the nearby organs and hemorrhage are the major hindrances of this procedure to manage urolithiasis specifically in children (144).

Open surgery

This therapeutic modality is recommended when other available advanced modalities to manage urolithiasis did not work and when there is large stone associated with many complications which could be life threatens for patient. In open surgery to remove the renal stone only single large incision is made. Sever hemorrhage and pain are the most common complications of this procedure (135, 145).

Conclusion

Renal stones are a major health issue among Pakistan population as well as worldwide. If it is not diagnosed properly and timely, it can become a very painful situation. A poor lifestyle like an inadequate amount of water intake, increased intake of protein as well as climate changes in this region of the world are the major reasons to develop renal stones. Some factors involved in the prompt treatment of renal stones such as late presentation, poverty, ignorance, non-accessibility of modern diagnostic methods. Morbidity rate of renal stones is increasing because of the late diagnosis, late seeking for medical help. Timely diagnosis and use of modern diagnostic tools will reduce morbidity and mortality. Health education of community regarding water intake and early treatment of stones will prove useful as preventive measures. Therefore, by reducing and identifying the risk factors and evaluating the patient, it is possible to improve the prognosis as far as the morbidity and mortality of renal stones patients. It could be concluded that aggressive screening and awareness programs should be arranged. Risk factors predisposing to the high incidence of renal stones should be identified and dealt with. Variation in climate and dietary habits should be regulated in preventing the development of renal stones.

Future prospects

Although strategies at major levels are required urgently to control calculi formation to improve the health status of the local population some community based health education programs are therefore also urgently needed, which gives awareness regarding proper water intake and healthy nutrition. Emphasis should be given on prevention and timely diagnosis of renal stones so that to give the patients better opportunities for renal stones treatment. Plantation of trees which have a long life with low water intake requirements should be planted to control sudden changes in the environment.

Abbreviation

Not used

Declarations

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References
1. Patle A, Hatware KV, Patil K, Sharma S, Gupta G. Role of herbal medicine in the management of urolithiasis—A review for future perspectives. Journal of Environmental Pathology, Toxicology and Oncology. 2019;38(2).
2. Abbagani S, Gundimeda SD, Varre S, Ponnala D, Mundluru HP. Kidney stone disease: etiology and evaluation. International Journal of Applied Biology and Pharmaceutical Technology. 2010;1(1):175-82.
3. Goldfarb DS, Fischer ME, Keich Y, Goldberg J. A twin study of genetic and dietary influences on nephrolithiasis: a report from the Vietnam Era Twin (VET) Registry. Kidney international. 2005;67(3):1053-61.
4. Parmar MS. Kidney stones. BMJ: British Medical Journal. 2004;328(7453):1420.
5. Gross CJ, Stiles JE, Savaiano DA. Effect of nutritional state and allopourinol on purine metabolism in the rat small intestine. Biochimica et Biophysica Acta (BBA)-General Subjects. 1988;966(1):168-75.
6. Raju DL, Cantarovich M, Brisson M-L, Tchervenkov J, Lipman ML. Primary hyperoxaluria: Clinical course, diagnosis, and treatment after kidney failure. American Journal of Kidney Diseases. 2008;51(1):e1-e5.
7. Pattanayak S, Mandal TK, Bandyopadhyay S. A study on use of plants to cure enteritis and dysentery in three southern districts of West Bengal, India. Journal of Medicinal Plants. 2015;3(5):277-83.
8. Honeck P, Wendt-Nordahl G, Krombach P, Bach T, Häcker A, Alken P, et al. Does open stone surgery still play a role in the treatment of urolithiasis? Data of a primary urolithiasis center. Journal of Endourology. 2009;23(7):1209-12.
9. Leighton T, Cleveland R. Lithotripsy. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine. 2010;224(2):317-42.
10. Kim SC, Kuo RL, Lingeman JE. Percutaneous nephrolithotomy: an update. Current opinion in urology. 2003;13(3):235-41.
11. Ramakumar S, Lancini V, Chan DY, Parsons JK, Kavoussi LR, Jarrett TW. Laparoscopic pyeloplasty with concomitant pyelolithotomy. The Journal of urology. 2002;167(3):1378-80.
12. Mandhani A, Kapoor R. Laparoscopic ureterolithotomy for lower ureteric stones: Steps to make it a simple procedure. Indian journal of urology: IJU: journal of the Urological Society of India. 2009;25(1):140.
13. Denstedt JD. Medical and surgical management of urolithiasis. Asian journal of urology. 2018;5(4):203.
14. Kale SS, Ghole VS, Pawar N, Jagtap DV. Inter-annual variability of urolithiasis epidemic from semi-arid part of Deccan Volcanic Province, India: climatic and hydrogeochemical perspectives. International journal of environmental health research. 2014;24(3):278-89.
15. Iguchi M, Umekawa T, Katoh Y, Kohri K, Kurita T. Prevalence of urolithiasis in Kaizuka City, Japan—an epidemiologic study of urinary stones. International journal of urology. 1996;3(3):175-9.
16. Calabrese V, Cornelius C, Dinkova-Kostova AT, Iavicoli I, Di Paola R, Koverech A, et al. Cellular stress responses, hormetic phytochemicals and vitagenes in aging and longevity. Biochimica et Biophysica Acta (BBA)-

Molecular Basis of Disease. 2012;1822(5):753-83.
17. Novikov A, Nazarov T, Startsev VY. Epidemiology of stone disease in the Russian Federation and Post-Soviet era. Urolithiasis: Springer; 2012. p. 97-105.
18. Ganesamoni R, Singh SK. Epidemiology of stone disease in Northern India. Urolithiasis: Springer; 2012. p. 39-46.
19. Vinarova L, Vinarov Z, Tcholakova S, Denkov ND, Stoyanov S, Lips A. The mechanism of lowering cholesterol absorption by calcium studied by using an in vitro digestion model. Food & function. 2016;7(1):151-63.
20. Memon A, Anwar K, Orakzai N, Ather MH, Biyabani SR, Nasir AR, et al. Epidemiology of stone disease in Pakistan. Urolithiasis: Springer; 2012. p. 21-38.
21. Singh P, Barjatiya M, Dhing S, Bhatnagar R, Kothari S, Dhar V. Evidence suggesting that high intake of fluoride provokes nephrolithiasis in tribal populations. Urological research. 2001;29(4):238-44.
22. Yasui T, Iguchi M, Suzuki S, Kohri K. Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. Urology. 2008;71(2):209-13.
23. SILVA GRN, MACIEL LC. Epidemiology of urolithiasis consultations in the Paraíba Valley. Revista do Colégio Brasileiro de Cirurgiões. 2016;43(6):410-5.
24. Freeg MAHA, Sreedharan J, Muttappallymyalil J, Venkatramana M, Shaafie IA, Mathew E, et al. A retrospective study of the seasonal pattern of urolithiasis. Saudi journal of kidney diseases and transplantation. 2012;23(6):1232.
25. Andreassen KH, Pedersen KV, Osther SS, Jung HU, Lildal SK, Osther PJS. How should patients with cystine stone disease be evaluated and treated in the twenty-first century? Urolithiasis. 2016;44(1):65-76.
26. AL-HUNAYAN A, ABDUL-HALIM H, Kehinde EO, AL-AWADI K, El Barky E, AL-ATEEQUI A. Mode of presentation and first line of management of non-recurrent urolithiasis in Kuwait. International journal of urology. 2004;11(11):963-8.
27. Afaj AH, Sultan MA. Mineralogical composition of the urinary stones from different provinces in Iraq. The Scientific World Journal. 2005;5:24-38.
28. Yapanoglu T, Demirel A, Adanur Ş, Yüksel H, Polat Ö. X-ray diffraction analysis of urinary tract stones. Turkish Journal of Medical Sciences. 2010;40(3):415-20.
29. Wu W, Yang D, Tiselius H-G, Ou L, Liang Y, Zhu H, et al. The characteristics of the stone and urine composition in Chinese stone formers: primary report of a single-center results. Urology. 2014;83(4):732-7.
30. گوگانی ش, بهروز, گرمی ق, اله ک, زاده ن, عزت. Chemical composition and epidemiological risk factors of urolithiasis in Ardabil Iran. Research Journal of Biological Sciences. 2008;3(6):620-6.
31. Pendse A, Singh P. The etiology of urolithiasis in Udaipur (Western part of India). Urological research. 1986;14(2):59-62.
32. Alatab S, Pourmand G, El Howairis MEF, Buchholz N, Najafi I, Pourmand MR, et al. National Profiles of Urinary Calculi A comparison Between Developing and Developed Worlds. Iranian journal of kidney diseases. 2016;10(2):51.
33. Alatab S, Pourmand G, El Howairis MEF, Buchholz N, Najafi I, Pourmand MR, et al. NATIONAL PROFILES OF URINARY CALCULI (A COMPARISON BETWEEN DEVELOPING AND DEVELOPED WORLDS). 2016.
34. Ansari MS, Gupta NP, Hemal AK, Dogra PN, Seth A, Aron M, et al. Spectrum of stone composition: structural analysis of 1050 upper urinary tract calculi from northern India. International journal of urology. 2005;12(1):12-6.
35. Ahmad F, Nada MO, Farid AB, Haleem M, Razack S. Epidemiology of urolithiasis with emphasis on ultrasound detection: A retrospective analysis of 5371 cases in Saudi Arabia. Saudi Journal of Kidney Diseases and Transplantation. 2015;26(2):386.
36. Hussain M. Enormity of urolithiasis in Sindh province. J Pak Med Assoc. 2014;64:1337-8.
37. Rizvi SA, Sultan S, Zafar MN, Ahmed B, Faiq SM, Hossain KZ, et al. Evaluation of children with

urolithiasis. Indian journal of urology: IJU: journal of the Urological Society of India. 2007;23(4):420.
38. Memon JM, Athar MA, Akhund AA. Clinical pattern of urinary stone disease in our setting. Annals of King Edward Medical University. 2009;15(1):17-.
39. Naqvi S, Rizvi S, Shahjehan S. Bladder stone disease in children, clinical studies. J Pak Med Assoc. 1984;34:94-101.
40. Hussain M, Lal M, Ali B, Naqvi S, Rizvi S. Urolithiasis in Sindh: a single centre experience with a review of 10,000 cases. J Nephrol Urol Transplant. 1998;1:10-3.
41. Shar A, Kazi Y, Soomro I, Zardari M. Bacteriological quality of drinking water of Sukkur City. Pakistan Journal of Medical Research. 2009;48(4):88-90.
42. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. American Journal of Epidemiology. 1996;143(3):240-7.
43. Abbas F, Khan R, Talati JJ, Afzal M, Rizvi I. The prevalence of silent kidney stones-an ultrasonographic screening study. Journal of Pakistan Medical Association. 2003;53(1):24.
44. Naqvi R, Ahmed E, Akhtar F, Yazdani I, Naqvi N, Rizvi A. Analysis of factors causing acute renal failure. JPMA The Journal of the Pakistan Medical Association. 1996;46(2):29-30.
45. Hussain M, Rizvi SAH, Askari H, Sultan G, Lal M, Ali B, et al. Management of stone disease: 17 years experience of a stone clinic in a developing country. Hypertension. 2009;6819:17.6.
46. Rizvi S, Naqvi SA. Renal replacement therapy in Pakistan. Saudi Journal of Kidney Diseases and Transplantation. 1996;7(4):404.
47. Rizvi S, Naqvi S, Hussain Z, Hashmi A, Hussain M, Zafar M, et al. Pediatric urolithiasis: developing nation perspectives. The Journal of urology. 2002;168(4):1522-5.
48. Mortazavi F, Mahbubi L. Clinical features and risk factors of pediatric urolithiasis. Iranian Journal of Pediatrics. 2007;17(2):129-33.
49. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. Journal of nephrology. 2001;13:S45-S50.
50. Daudon M. Epidémiologie actuelle de la lithiase rénale en France.[Epidemiology of nephrolithiasis in France]. Ann Urol(Paris). 2005:209-31.
51. Smith LH, Fromm H, Hofmann AF. Acquired hyperoxaluria, nephrolithiasis, and intestinal disease: description of a syndrome. New England Journal of Medicine. 1972;286(26):1371-5.
52. Bush NC, Xu L, Brown BJ, Holzer MS, Gingrich A, Schuler B, et al. Hospitalizations for pediatric stone disease in United States, 2002–2007. The Journal of urology. 2010;183(3):1151-6.
53. VanDervoort K, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, et al. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. The Journal of urology. 2007;177(6):2300-5.
54. Copelovitch L. Urolithiasis in children: medical approach. Pediatric Clinics. 2012;59(4):881-96.
55. Agarwal S, Dash S. Spectrum of renal diseases in Indian adults. The Journal of the Association of Physicians of India. 2000;48(6):594-600.
56. Sarkissian A, Babloyan A, Arikyants N, Hesse A, Blau N, Leumann E. Pediatric urolithiasis in Armenia: a study of 198 patients observed from 1991 to 1999. Pediatric Nephrology. 2001;16(9):728-32.
57. Stamatiou K, Karanasiou V, Lacroix R, Kavouras N, Papadimitriou V, Chlopsios C, et al. Prevalence of urolithiasis in rural Thebes, Greece. Rural Remote Health. 2006;6(4):610.
58. Paterson R, Fernandez A, Razvi H, Sutton R. Evaluation and medical management of the kidney stone patient. Canadian Urological Association Journal. 2010;4(6):375.
59. Pietrow PK, Karellas M. Medical management of common urinary calculi. South African Family Practice. 2007;49(3):44-8.
60. Nicoletta JA, Lande MB. Medical evaluation and treatment of urolithiasis. Pediatric Clinics. 2006;53(3):479-91.
61. Leehey DJ, Moinuddin I. Handbook of nephrology: Lippincott Williams & Wilkins; 2019.
62. Hechtman L. Clinical naturopathic medicine: Elsevier Health Sciences; 2018.

63. Scheinman SJ. Urinary calculi. Medicine. 2003;31(6):77-80.
64. Thomas B, Hall J. Urolithiasis. Surgery (Oxford). 2005;23(4):129-33.
65. Kambadakone AR, Eisner BH, Catalano OA, Sahani DV. New and evolving concepts in the imaging and management of urolithiasis: urologists' perspective. Radiographics. 2010;30(3):603-23.
66. Ajayi L, Jaeger P, Robertson W, Unwin R. Renal stone disease. Medicine. 2007;35(8):415-9.
67. Rathod N, Biswas D, Chitme H, Ratna S, Muchandi I, Chandra R. Anti-urolithiatic effects of Punica granatum in male rats. Journal of ethnopharmacology. 2012;140(2):234-8.
68. Mandel NS, Mandel GS. Physicochemistry of urinary stone formation. Renal Stone Disease: Springer; 1987. p. 1-24.
69. Thomson JM, Glocer J, Abbott C, Maling TM. Computed tomography versus intravenous urography in diagnosis of acute flank pain from urolithiasis: a randomized study comparing imaging costs and radiation dose. Australasian radiology. 2001;45(3):291-7.
70. Portis AJ, Sundaram CP. Diagnosis and initial management of kidney stones. American family physician. 2001;63(7):1329-40.
71. Biyani C, Joyce A. Urolithiasis in pregnancy. I: pathophysiology, fetal considerations and diagnosis. BJU international. 2002;89(8):811-8.
72. Wilkinson B, Hall J. Management of stone disease. Surgery (Oxford). 2010;28(7):338-44.
73. Chen Y-T. Urolithiasis update: Evaluation and management. Urological Science. 2012;23(1):5-8.
74. Andrabi Y, Patino M, Das CJ, Eisner B, Sahani DV, Kambadakone A. Advances in CT imaging for urolithiasis. Indian journal of urology: IJU: journal of the Urological Society of India. 2015;31(3):185.
75. Worster A, Preyra I, Weaver B, Haines T. The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis. Annals of emergency medicine. 2002;40(3):280-6.
76. Villa L, Giusti G, Knoll T, Traxer O. Imaging for urinary stones: update in 2015. European urology focus. 2016;2(2):122-9.
77. Vrtiska TJ, Krambeck AE, McCollough CH, Leng S, Qu M, Yu L, et al. Imaging evaluation and treatment of nephrolithiasis: an update. Minnesota medicine. 2010;93(8):48.
78. Patel D, Patel U. Urolithiasis: the role of imaging. Trends in Urology & Men's Health. 2012;3(3):25-8.
79. Neisius A, Astroza GM, Wang C, Nguyen G, Kuntz NJ, Januzis N, et al. Digital tomosynthesis: a new technique for imaging nephrolithiasis. Specific organ doses and effective doses compared with renal stone protocol noncontrast computed tomography. Urology. 2014;83(2):282-7.
80. McKenzie G, Hall J. Management of stone disease. Surgery (Oxford). 2013;31(7):354-61.
81. Malhotra K. Medical aspects of renal stones. Journal Indian Academy of Clinical Medicine. 2008;9(4):282.
82. O'Donoghue P, McSweeney S, Jhaveri K. Genitourinary imaging: current and emerging applications. Journal of postgraduate medicine. 2010;56(2):131.
83. Strohmaier WL. Imaging in pediatric urolithiasis—what's the best choice? Translational pediatrics. 2015;4(1):36.
84. Kaplon DM, Sterrett S, Nakada SY. Medical management of acute urolithiasis in one American academic emergency room. BJU international. 2010;105(6):856-8.
85. Seitz C, Liatsikos E, Porpiglia F, Tiselius H-G, Zwergel U. Medical therapy to facilitate the passage of stones: what is the evidence? European urology. 2009;56(3):455-71.
86. Michel MC, de la Rosette JJ. alpha-blocker treatment of urolithiasis. European urology. 2006;50(2):213.
87. Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of ureteral calculi. Annals of emergency medicine. 2007;50(5):552-63.
88. Hollingsworth JM, Rogers MA, Kaufman SR, Bradford TJ, Saint S, Wei JT, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. The Lancet. 2006;368(9542):1171-9.
89. Romics I. The role of alpha-adrenoreceptors in the treatment of urological diseases. Neurochemistry international. 2007;51(5):328-31.

90. Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology. 2012.
91. Finkielstein VA, Goldfarb DS. Strategies for preventing calcium oxalate stones. Cmaj. 2006;174(10):1407-9.
92. Pak CY. Etiology and treatment of urolithiasis. American journal of kidney diseases. 1991;18(6):624-37.
93. Grases F, Prieto RM, Fernandez-Cabot RA, Costa-Bauzá A, Tur F, Torres JJ. Effects of polyphenols from grape seeds on renal lithiasis. Oxidative medicine and cellular longevity. 2015;2015.
94. Heilberg IP, Schor N. Renal stone disease: causes, evaluation and medical treatment. Arquivos Brasileiros de Endocrinologia & Metabologia. 2006;50(4):823-31.
95. Singh SK, Agarwal MM, Sharma S. Medical therapy for calculus disease. BJU international. 2011;107(3):356-68.
96. Moe OW. Kidney stones: pathophysiology and medical management. The lancet. 2006;367(9507):333-44.
97. Moran ME, Abrahams HM, Burday DE, Greene TD. Utility of oral dissolution therapy in the management of referred patients with secondarily treated uric acid stones. Urology. 2002;59(2):206-10.
98. Spernat D, Kourambas J. Urolithiasis–medical therapies. BJU international. 2011;108:9-13.
99. Lotan Y. Medical management strategies to prevent recurrent nephrolithiasis are stagnant and stronger evidence is needed to reduce morbidity. BMJ Evidence-Based Medicine. 2014;19(1):12-.
100. Atmani F, Slimani Y, Mimouni M, Hacht B. Prophylaxis of calcium oxalate stones by Herniaria hirsuta on experimentally induced nephrolithiasis in rats. BJU international. 2003;92(1):137-40.
101. Korets R, Graversen JA, Gupta M. Dissolution of stones by oral and irrigative therapy. Urolithiasis: Springer; 2012. p. 533-7.
102. Bernardo NO, Smith AD. Chemolysis of urinary calculi. Urologic Clinics of North America. 2000;27(2):355-65.
103. Becker G. Uric acid stones. Nephrology. 2007;12:S21-S5.
104. Elkoushy MA, Violette PD, Andonian S. Percutaneous instillation of chemolytic, chemotherapeutic, and antifungal agents. Smith's Textbook of Endourology. 2012:290-309.
105. Xiang-bo Z, Zhi-ping W, Jian-min D, Jian-zhong L, Bao-liang M. New chemolysis for urological calcium phosphate calculi–a study in vitro. BMC urology. 2005;5(1):9.
106. Heimbach D, Bäumler D, Schoeneich G, Hesse A. Percutaneous chemolysis—An important tool in the treatment of urolithiasis. International urology and nephrology. 1998;30(6):655-64.
107. Bihl G, Meyers A. Recurrent renal stone disease—advances in pathogenesis and clinical management. The Lancet. 2001;358(9282):651-6.
108. Micali S, Grande M, Sighinolfi MC, Carne CD, Stefani SD, Bianchi G. Medical therapy of urolithiasis. Journal of endourology. 2006;20(11):841-7.
109. Pak CY. Medical management of nephrolithiasis. The Journal of urology. 1982;128(6):1157-64.
110. Pareta SK, Patra KC, Mazumder PM, Sasmal D. Aqueous extract of Boerhaavia diffusa root ameliorates ethylene glycol-induced hyperoxaluric oxidative stress and renal injury in rat kidney. Pharmaceutical biology. 2011;49(12):1224-33.
111. Tiwari A, Soni V, Londhe V, Bhandarkar A, Bandawane D, Nipate S. An overview on potent indigenous herbs for urinary tract infirmity: urolithiasis. Asian J Pharm Clin Res. 2012;5(1):7-12.
112. Pareta SK, Patra KC, Mazumder PM, Sasmal D. Establishing the principle of herbal therapy for antiurolithiatic activity: A review. J Pharmacol Toxicol. 2011;6(3):321-32.
113. Trinchieri A, Lizzano R, Bernardini P, Nicola M, Pozzoni F, Romano A-L, et al. Effect of acute load of grapefruit juice on urinary excretion of citrate and urinary risk factors for renal stone formation. Digestive and Liver Disease. 2002;34:S160-S3.
114. Seltzer MA, Low RK, McDonald M, Shami GS, Stoller ML. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. The Journal of urology. 1996;156(3):907-9.
115. Han X, Shen T, Lou H. Dietary polyphenols and their biological significance. International journal of molecular sciences. 2007;8(9):950-88.

116. Mendoza-Wilson AM, Glossman-Mitnik D. Theoretical study of the molecular properties and chemical reactivity of (+)-catechin and (−)-epicatechin related to their antioxidant ability. Journal of Molecular Structure: THEOCHEM. 2006;761(1-3):97-106.
117. Higdon JV, Frei B. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. 2003.
118. Amengual-Cladera E, Nadal-Casellas A, Gómez-Pérez Y, Gomila I, Prieto RM, Proenza AM, et al. Phytotherapy in a rat model of hyperoxaluria: the antioxidant effects of quercetin involve serum paraoxonase 1 activation. Experimental Biology and Medicine. 2011;236(10):1133-8.
119. Khan SA, Priyamvada S, Farooq N, Khan S, Khan MW, Yusufi AN. Protective effect of green tea extract on gentamicin-induced nephrotoxicity and oxidative damage in rat kidney. Pharmacological Research. 2009;59(4):254-62.
120. Zhai W, Zheng J, Yao X, Peng B, Liu M, Huang J, et al. Catechin prevents the calcium oxalate monohydrate induced renal calcium crystallization in NRK-52E cells and the ethylene glycol induced renal stone formation in rat. BMC complementary and alternative medicine. 2013;13(1):228.
121. Kanlaya R, Singhto N, Thongboonkerd V. EGCG decreases binding of calcium oxalate monohydrate crystals onto renal tubular cells via decreased surface expression of alpha-enolase. JBIC Journal of Biological Inorganic Chemistry. 2016;21(3):339-46.
122. Nirumand M, Hajialyani M, Rahimi R, Farzaei M, Zingue S, Nabavi S, et al. Dietary plants for the prevention and management of kidney stones: preclinical and clinical evidence and molecular mechanisms. International journal of molecular sciences. 2018;19(3):765.
123. Noorafshan A, Karbalay-Doust S, Karimi F. Diosmin reduces calcium oxalate deposition and tissue degeneration in nephrolithiasis in rats: a stereological study. Korean journal of urology. 2013;54(4):252-7.
124. Crespo M, Galvez J, Cruz T, Ocete M, Zarzuelo A. Anti-inflammatory activity of diosmin and hesperidin in rat colitis induced by TNBS. Planta medica. 1999;65(07):651-3.
125. Rehman MU, Tahir M, Khan AQ, Khan R, Lateef A, Hamiza OO, et al. Diosmin protects against trichloroethylene-induced renal injury in Wistar rats: plausible role of p53, Bax and caspases. British Journal of Nutrition. 2013;110(4):699-710.
126. Prabhu VV, Sathyamurthy D, Ramasamy A, Das S, Anuradha M, Pachiappan S. Evaluation of protective effects of diosmin (a citrus flavonoid) in chemical-induced urolithiasis in experimental rats. Pharmaceutical biology. 2016;54(9):1513-21.
127. Pastukhov AV, Levchenko LA, Sadkov AP. Spectroscopic study on binding of rutin to human serum albumin. Journal of Molecular Structure. 2007;842(1-3):60-6.
128. Ghodasara J, Pawar A, Deshmukh C, Kuchekar B. Inhibitory effect of rutin and curcumin on experimentally-induced calcium oxalate urolithiasis in rats. Pharmacognosy research. 2010;2(6):388.
129. Zhu W, Xu Y-f, Feng Y, Peng B, Che J-p, Liu M, et al. Prophylactic effects of quercetin and hyperoside in a calcium oxalate stone forming rat model. Urolithiasis. 2014;42(6):519-26.
130. Sarica K. Medical aspect and minimal invasive treatment of urinary stones in children. ARCHIVIO ITALIANO DI UROLOGIA ANDROLOGIA. 2008;80(2):43.
131. Chaussy C, Bergsdorf T. Extracorporeal shockwave lithotripsy for lower pole calculi smaller than one centimeter. Indian journal of urology: IJU: journal of the Urological Society of India. 2008;24(4):517.
132. Neisius A, Wöllner J, Thomas C, Roos FC, Brenner W, Hampel C, et al. Treatment efficacy and outcomes using a third generation shockwave lithotripter. BJU international. 2013;112(7):972-81.
133. Gayer G, Hertz M, Stav K, Zissin R, editors. Minimally invasive management of urolithiasis. Seminars in Ultrasound, CT and MRI; 2006: Elsevier.
134. Papatsoris AG, Skolarikos A, Buchholz N. Intracorporeal laser lithotripsy. Arab journal of urology. 2012;10(3):301-6.
135. Morton AR, Iliescu EA, Wilson JW. Nephrology: 1. Investigation and treatment of recurrent kidney stones. Cmaj. 2002;166(2):213-8.
136. Skolarikos AA, Papatsoris AG, Mitsogiannis IC, Chatzidarellis L, Liakouras C, Deliveliotis C. Current

status of ureteroscopic treatment for urolithiasis. International journal of urology. 2009;16(9):713-7.
137. Zhong W, Yang B, He F, Wang L, Swami S, Zeng G. Surgical management of urolithiasis in patients after urinary diversion. PloS one. 2014;9(10):e111371.
138. Kijvikai K. The role of laparoscopic surgery for renal calculi management. Therapeutic advances in urology. 2011;3(1):13-8.
139. Nadu A, Schatloff O, Morag R, Ramon J, Winkler H. Laparoscopic surgery for renal stones: is it indicated in the modern endourology era? International braz j urol. 2009;35(1):9-18.
140. Celik H, Tasdemir C, Altintas R. An overview of percutaneous nephrolithotomy. EMJ Urol. 2015;1:46-52.
141. Manjula K, Pazhanichami K, Rajendran K, Kumaran S, Eevera T. Herbal remedy for urinary stones. Vegetables and human health Jodhpur (India): Scientific Publisher. 2015:454-68.
142. Bawari S, Sah AN, Tewari D. Urolithiasis: an update on diagnostic modalities and treatment protocols. Indian Journal of Pharmaceutical Sciences. 2017;79(2):164-74.
143. Ritter M, Krombach P, Michel MS. Percutaneous stone removal. European Urology Supplements. 2011;10(5):433-9.
144. Horuz R, Sarica K. The management of staghorn calculi in children. Arab journal of urology. 2012;10(3):330-5.
145. El-Husseiny T, Buchholz N. The role of open stone surgery. Arab journal of urology. 2012;10(3):284-8.
146. Yoshida O, Okada Y. Epidemiology of urolithiasis in Japan: a chronological and geographical study. Urologia internationalis. 1990;45(2):104-11.
147. Yoshida O, Terai A, Ohkawa T, Okada Y. National trend of the incidence of urolithiasis in Japan from 1965 to 1995. Kidney international. 1999;56(5):1899-904.
148. Yanagawa M, Kawamura J, Onishi T, Soga N, Kameda K, Sriboonlue P, et al. Incidence of urolithiasis in northeast Thailand. International journal of urology. 1997;4(6):537-40.
149. Sreenevasan G. Urinary stones in Malaysia--its incidence and management. The Medical journal of Malaysia. 1990;45(2):92-112.
150. Thalut K, Rizal A, Brockis J, Bowyer R, Taylor T, Wisniewski Z. The endemic bladder stones of Indonesia---epidemiology and clinical features. British journal of urology. 1976;48(7):617-21.
151. Salem S, ABU E. The incidence of renal colic and calculi in Kuwait. An epidemiológical study. Journal Medical Libanais. 1969;22(16):747-55.
152. Shajari A, Sanjerehei MM. Modeling the distribution of urolithiasis prevalence under projected climate change in Iran. Urolithiasis. 2015;43(4):339-47.
153. Ketabchi AA, Aziziolahi GA. Prevalence of symptomatic urinary calculi in Kerman, Iran. Urology journal. 2008;5(3):156-60.
154. Pugliese JM, Baker KC. Epidemiology of nephrolithiasis in personnel returning from Operation Iraqi Freedom. Urology. 2009;74(1):56-60.
155. Semins MJ, Matlaga BR. Medical evaluation and management of urolithiasis. Therapeutic advances in urology. 2010;2(1):3-9.
156. Bandi G, Nakada SY, Penniston KL. Practical approach to metabolic evaluation and treatment of the recurrent stone patient. Wisconsin Medical Journal (WMJ). 2008;107(2):91.
157. Reynolds T. Best Practice No 181: Chemical pathology clinical investigation and management of nephrolithiasis. Journal of clinical pathology. 2005;58(2):134-40.
158. Schumacher Jr HR, Becker MA, Wortmann RL, MacDonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Care & Research. 2008;59(11):1540-8.
159. Garcia-Valladares I, Khan T, Espinoza LR. Efficacy and safety of febuxostat in patients with hyperuricemia and gout. Therapeutic advances in musculoskeletal disease. 2011;3(5):245-53.
160. Brardi S, Imperiali P, Cevenini G, Verdacchi T, Ponchietti R. Effects of the association of potassium

citrate and agropyrum repens in renal stone treatment: results of a prospective randomized comparison with potassium citrate. Arch Ital Urol Androl. 2012;84(2):61-7.
161. Pareta SK, Patra KC, Mazumder PM, Sasmal D. Boerhaavia diffusa Linn AQUEOUS EXTRACT AS CURATIVE AGE TI ETHYLE E GLYCOL I DUCED UROLITHIASIS.
162. Cho HJ, Bae WJ, Kim SJ, Hong SH, Lee JY, Hwang T-K, et al. The inhibitory effect of an ethanol extract of the spores of Lygodium japonicum on ethylene glycol-induced kidney calculi in rats. Urolithiasis. 2014;42(4):309-15.
163. Akanae W, Tsujihata M, Yoshioka I, Nonomura N, Okuyama A. Orthosiphon grandiflorum has a protective effect in a calcium oxalate stone forming rat model. Urological research. 2010;38(2):89-96.
164. Vyas B, Vyas R, Joshi S, Santani D. Antiurolithiatic activity of whole-plant hydroalcoholic extract of Pergularia daemia in rats. Journal of young pharmacists. 2011;3(1):36-40.
165. Moriyama MT, Suga K, Miyazawa K, Tanaka T, Higashioka M, Noda K, et al. Inhibitions of urinary oxidative stress and renal calcium level by an extract of Quercus salicina Blume/Quercus stenophylla Makino in a rat calcium oxalate urolithiasis model. International journal of urology. 2009;16(4):397-401.
166. Mirian E-CM, Juanita N-M, Christophe BO, Estela M-CM. Molecular mechanisms involved in the protective effect of the chloroform extract of Selaginella lepidophylla (Hook. et Grev.) Spring in a lithiasic rat model. Urolithiasis. 2013;41(3):205-15.

Table 1: Prevalence and major constituents of urolithiasis in developed and developing countries

Countries	**Years**	**Composition of stone**	**Prevalence (%)**	**References**
Japan	1945-1987	Calcium Oxalate, Uric Acid, Cystine, Struvite	5.4	(146)
Japan	1992	Calcium Oxalate	6.95	(15)
Japan	1965-1995	Calcium Oxalate	4.3-9.0	(147)
Russia	1980-2008	Calcium Oxalate, Calcium Phosphate, Uric Acid, Cystine,	2-3	(17)
India	1994-2008	Calcium Oxalate	0.3 -9.3	(14)
India	2010-2012	Calcium Oxalate	0.3-7.6	(23)
Pakistan	1975-2010	Calcium Oxalate, Calcium Phosphate, Uric Acid, Cystine, Struvite, Apatite	16	(20)
Thailand	1997	Calcium Oxalate	16.9	(148)
Malaysia	1962-1981	Calcium Oxalate, Uric Acid, Cystine, Struvite	2.2-4.2	(149)
Indonesia	1976	Calcium Oxalate, Struvite	0.09	(150)
Saudi Arabia	2004-2008	Calcium Oxalate, Calcium Phosphate, Uric Acid	19.1	(35)
Kuwait	1966-1968	Calcium Oxalate, Calcium Phosphate, Uric Acid	4-5	(151)
Iran	2005	Calcium Oxalate, Calcium Phosphate, Uric Acid, Struvite	6.1	(152)
Iran	2005-2006	Calcium Oxalate, Calcium	8.1	(153)

		Phosphate, Uric Acid, Struvite		
Iraq	2005	Calcium Oxalate, Calcium Phosphate, Uric Acid	1	(154)

Table 2: Different therapeutic Modalities for the management of Urolithiasis

SYNTHETIC DRUGS FOR UROLITHIASIS		
Drugs	**Mechanism of Action and Types of stones treated**	**References**
Thiazide diuretics	Diuretics, decrease excretion of calcium, Calcium oxalate, calcium phosphate Stones	(90); (155)
Potassium phosphate	Dissolution of stones by chelation Calcium oxalate stones	(98)
Sodium cellulose phosphate	Decrease the intestinal absorption of calcium Calcium oxalate stones	(156)
Allopurinol	Diuretics, xanthine oxidase inhibitor Uric acid stones	(93)
D-penicillamine	Dissolution of stone by chelation, Cystine stones	(98, 157)
Febuxostat	Xanthine oxidase inhibitor Uric acid stones	(158)(159)
Potassium citrate	Diuretics, Make soluble citrate calcium, prevent deposition of calcium phosphate, uric acid and calcium oxalate	(96, 156)
Alpha blockers	Inhibition of ureteral smooth muscle contractions to exert expulsive pressure Ureteral stones	(98)
Alpha mercaptopropionylglycine	Dissolution of stone by chelation Cystine stones	(98)
Acetohydroxamic acid	Inhibitor of urease enzyme Struvite stones	(Bandi et al., 2008)
Calcium channel blockers	Inhibition of ureteral smooth muscle contractions to exert expulsive pressure Ureteral stones	(Seitz et al., 2009)
Acetazolamide	Alkalization, chemolysis, Uric acid, cystine stones	(95)
Sodium bicarbonate	Diuretics, chemolysis, alteration of pH Uric acid stones	(98)
DIETARY AND MEDICINAL PLANTS FOR THE TREATMENT OF UROLITHISIS		
Medicinal and Dietary plants	**Mechanism of Action and Types of stones treated**	**References**

Agropyron repens	Antioxidant and dissolution of stones to decrease the size and number of uric acid stones	(160)
Boerhaavia diffusa	Has diuretic activity and decrease the excretion of oxalate and calcium	(161)
Cranbery juice	Contain citrate which make the calcium citrate and lowers the excretion of oxalate and calcium	(161)
Grapefriut juice	Also contain citrate which decrease the excretion of calcium and oxalate	(161)
Herniaria hersuta	Work as diuretic have antioxidant properties, help in the dissolution of pre-existing renal stones, decreases crystal size and increases COD	(161)
Lygodium japonicum	Increases urinary citrate levels, alter urine pH, antioxidant activities Peroxides of the renal decrease, oxalate, uric acid, calcium and deposits of oxalate decrease	(122, 162)
Orthosiphon grandiflorus	SOD and CAT activities are increased to lowers the renal crystal deposit	(163)
Pergularia daemia	Nephroprotective potential by decreasing the blood urea, creatinine, BUN and uric acid	(164)
Pyracantha crenulata	Antioxidant potential, dissolution activity, enhances the dieresis and decreases the constituents of stone formation	(161)
Quercus salicina	Reduces the oxidative stress, MDA and creatinine and renal calcium level	(165)
Selaginella lepidophylla	Enhances the rate of urine flow, GFR antioxidant potential, decrease the lipid-peroxidation and expression of renal cortical organic anion transporter (OAT3).	(166)
Tribulus terrestris	Potent diuretic, khellin and visnagin prevent renal epithelial cell damage caused by oxalate and COM	(161)
STONES FRAGMENTATION MODALITIES		
Medicinal and Dietary plants	**Mechanism of Action and Types of stones treated**	**References**
Extracorporeal shock wave lithotripsy	Minimally invasive fragmentation of stones Radiolucent calculi, Renal stones less than 2 cm, Ureteral stones less than 1 cm	(70)
Ureteroscopy	Invasive fragmentation of ureter stones	(130)

Percutaneous nephrolithotomy	Renal stones size more than 2 cm, Proximal ureteral stones size more than1 cm	(70)

Figure 1: Pathophysiology of the urolithiasis and the possible targets to prevent or treat the renal stone.

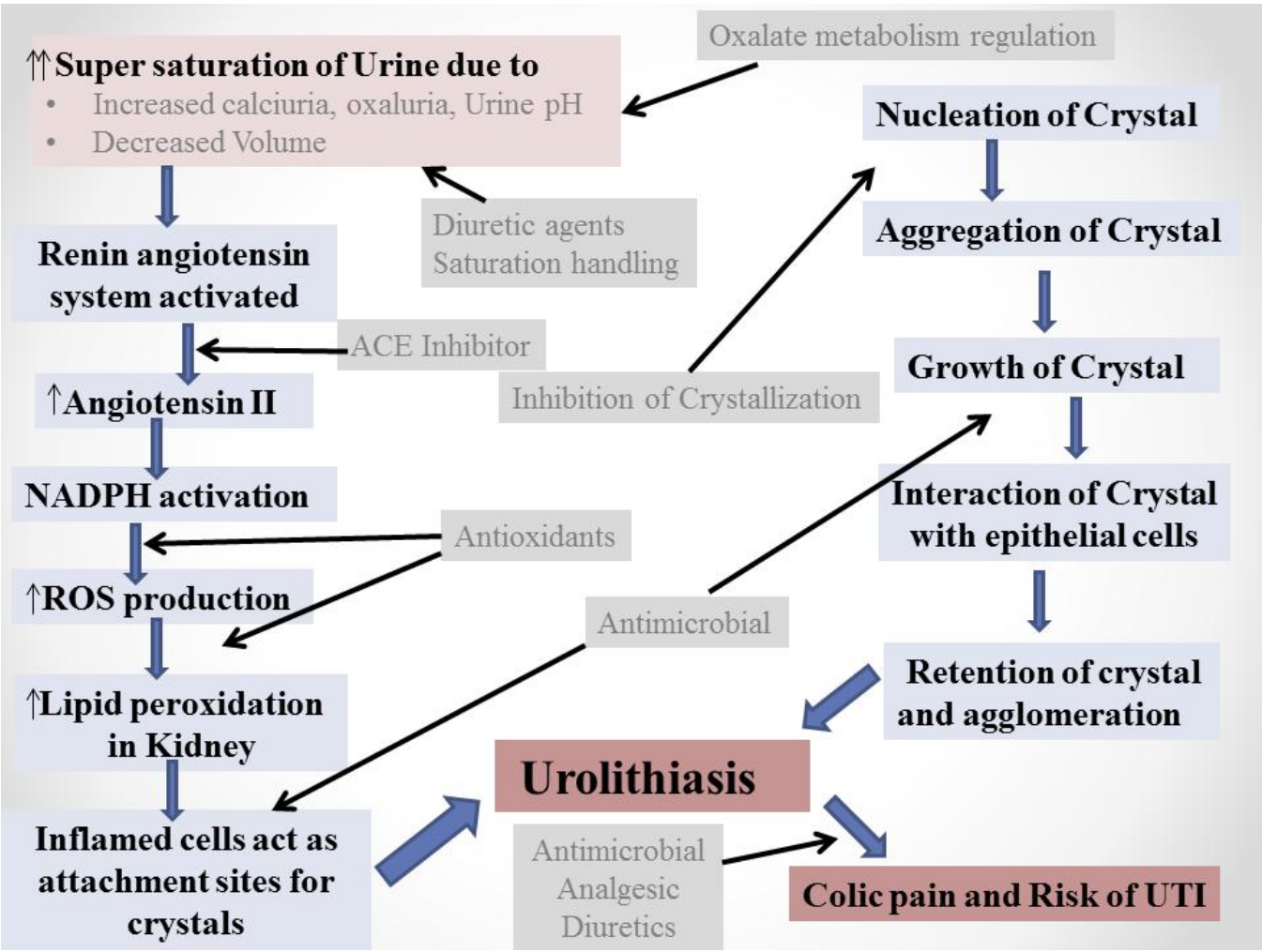

Figure 2: Diagrammatically representation of the anatomical location of calculi in the urinary tract.