IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
January 2020 Vol.:17, Issue:2

Comprehensive Review on Kidney Stone

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

PRADNYA NILESH JAGTAP*, PRANESH PANDURANG MEMANE, SAYALI SUNIL CHAVAN, RAVINDRA Y.PATIL

PDEA'S Seth Govind Raghunath Sable College Of Pharmacy, Saswad, Pune- 412301

Submission: 25 December 2019
Accepted: 31 December 2019
Published: 30 January 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Kidney Stone, Urolithiasis, Nephrolithiasis, Renal Calculi

ABSTRACT

Kidney stone disease is a crystal concretion formed usually within the kidneys. A kidney stone is the most common disease of the urinary tract. Now a day's large numbers of peoples affected with a kidney stone. Approximately 2 million people in India are affected with nephrolithiasis, urolithiasis every year. The chemical composition of kidney stones depends on abnormalities in the urine composition of a variety of chemicals. There are different kinds of renal stones and their correct identification is important in the selection of treatment. In the management of kidney stones, 2-3 lit/day fluid intake ensures the avoidance of kidney stones formation. Now a day's simple and reliable protocol is there to differentiate the various cause of stones.

INTRODUCTION

Kidney stone disease is a crystal concretion formed usually within the kidneys. Mankind has been afflicted by urinary stones for centuries dating back to 4000 B.C. and it is the most common disease of the urinary tract. The prevention of renal stone recurrence remains to be a serious problem in human health [1]. With its increasing prevalence, they are imposing a significant economic burden on both developing and developed nations. It has been observed that renal stones are associated with systemic diseases like Type 2 diabetes mellitus, obesity, dyslipidemia, and hypertension [2]. The use of topiramate, which is prescribed for the management of epilepsy, for migraine headache prophylaxis and as a weight-loss agent, has been associated with the development of metabolic acidosis, hypokalaemia and renal stone disease [5]. Metabolic syndrome (MetS) is the co-occurrence of metabolic abnormalities, including centrally distributed obesity, hypertension, dyslipidemia, and hyperglycemia with a concurrent rise in the incidence of kidney stone disease. The incidence of kidney stone disease is rising globally and some investigators have proposed a causal link between MetS and kidney stones [6]. Urinary lithiasis is a common disease with a lifetime risk of 12% in men and 5% in women. The incidence of the disease varies by age with peak occurrence between the ages of 20 and 40 years, sex with the highest risk among men (~10%), and ethnicity—with the highest risk among Caucasians [8]. In the last few decades, it has been widely documented that kidney stone disease is a global health problem that seriously affects human health. Kidney stone disease is common in the populations of industrialized countries [9]. Increased incidence of kidney stones in the industrialized world is associated with improved standards of living and is strongly associated with race or ethnicity and region of residence [17]. India, Pakistan and Southern China comprise an important part of the stone belt in Asia and the rest of the stone world [10]. The modern western lifestyle provides a host of factors that impair urine composition and thereby increase the risk of stone formation. In our everyday life, we do not drink enough water and only twice or thrice a day, we eat food that is too rich in calories and table salt, but has deficiencies in fiber and alkali. Last but not least, we do not exercise enough, recent work showed that being overweight is a crucial risk factor with significant impact on stone formation [11]. Kidney stone formation is a complex process and the result of a cascade of events, including crystal nucleation, growth, and aggregation, and crystal retention within the renal tubules [14]. Approximately 80% of stones are composed of calcium oxalate (CaOx) and calcium phosphate (CaP); 10% of struvite (magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme

urease), 9% of uric acid (UA); and the remaining 1% are composed of cystine or ammonium acid urate or are diagnosed as drug-related stones. Stones ultimately arise because of an unwanted phase change of these substances from liquid to solid state [19]. The formation of kidney stones is also known as renal calculi or crystal, In medical terminology condition of having urinary calculi is termed as nephrolithiasis and urolithiasis where the root word "Lith" meaning "a stone" [26]. This review summarises the pathophysiology of renal stones and discusses the clinical management for the prevention of renal stones.

Epidemiology of Kidney Stones:

A kidney stone is one of the oldest recorded disorders of human and one of the major health burdens. Now a day's large number of peoples are affected by this disorder all over the world. Three common terms used in an epidemiological study of renal calculi are incidence, prevalence and lifetime prevalence [26]. Globally, kidney stone disease prevalence and recurrence rates are increasing, with limited options of effective drugs. Urolithiasis affects about 12% of the world population at some stage in their lifetime. It affects all ages, sexes, and races but occurs more frequently in men than in women within the age of 20–49years [1][2]. Patients with kidney stone disease can have increased levels of bodily pain, depression, loss of days at work and increased anxiety and financial distress, leading to overall lower quality of life scores [7]. There are basic anatomical differences between kidneys of humans and those of animals such as dogs, rabbits, and rats; the latter has been extensively used to study renal ultrastructure and physiology and have been employed in the development of models of many renal diseases [14]. The incidence and prevalence rates of kidney stones may be affected by genetic, nutritional, and environmental factors. About 0·1–0·4% of the population is believed to have kidney stones every year in the USA and Europe; about 2–5% of the population in Asia, 8–15% in Europe and North America, and 20% in Saudi Arabia develop renal stones in their lifetime.1 Renal stones tend to recur, and the recurrence rate is about 75% during 20 years [18]. Approximate 2 million people in India are affected with nephrolithiasis every year and some parts of the country have name denoted as a stone belt that is, Gujarat, Maharashtra, Punjab, Rajasthan, Delhi, Haryana and part of states on North Eastside. Urinary stone is also found in south India due to the high intake of tamarind in a regular diet. In the upper urinary tract, urolithiasis is found mainly in the form of pure calcium oxalate crystals as observed in case studies of AIIMS, New Delhi [26].

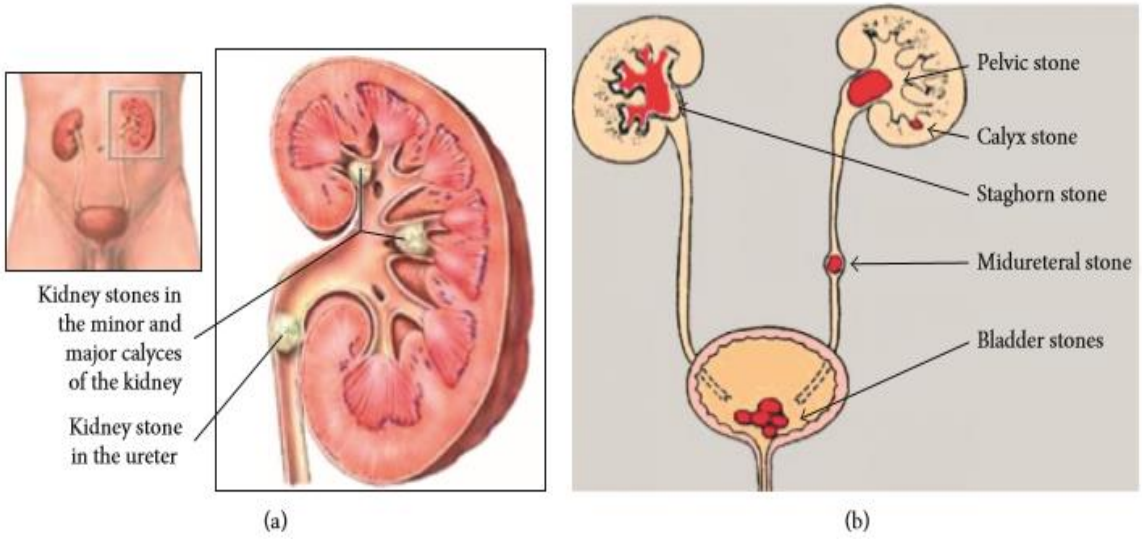

Figure No. 1: Kidney stone locations in the urinary system. (a) Adopted from. (b) Adopted from[1].

The Urinary System and Stones:

The urinary filtrate is formed in the glomerulus and passes into the tubules where the volume and content are altered by reabsorption or secretions. Most solute reabsorption occurs in the proximal tubules, whereas fine adjustments to urine composition take place in the distal tubule and collecting ducts. The loop of Henle serves to concentrate urine composed of 95% water, 2.5% urea, 2.5% mixture of minerals, salts, hormones, and enzymes. In the proximal tubules, glucose, sodium, chloride, and water are reabsorbed and returned to the bloodstream along with essential nutrients such as amino acids, proteins, bicarbonate, calcium, phosphate, and potassium. In the distal tubule, the salt and acid-base balance of blood are regulated [1]. Kidney stone formation is a nanobacterial disease analogous to helicobacter pylori infection and peptic ulcer disease [12]. Urinary calculi are solid particles in the urinary system. They may cause pain, nausea, vomiting, hematuria and possibly chills and fever due to secondary infection [27]. Abnormal urine pH and calcium excretion rate are predominant findings in SFs that play a major role in the pathogenesis of stone formation [19].

A different function of the urinary system:

- Excretion or elimination of metabolic waste product
- Regulation of fluid volume
- Regulation of different electrolytes

- Maintain the pH of the blood
- Homeostasis maintenance
- Elimination of toxins
- Separation of urea and mineral salts
- Mineral and salt balance [26]

Types of Kidney Stones:

The chemical composition of kidney stones depends on the abnormalities in the urine composition of various chemicals. Stones differ in size, shape, and chemical compositions (mineralogy). Based on variations in mineral composition and pathogenesis, kidney stones are commonly classified into five types as follows [1]. Stones along the urinary tract can be located in the kidneys, ureters and urinary bladder (Fig. 2). Kidney stones are categorized as either staghorn (filling numerous major and minor calyces) or non-staghorn. Non-staghorn stones are described as calyceal or pelvic in location, while ureteral stones are defined as proximal, middle or distal [16].

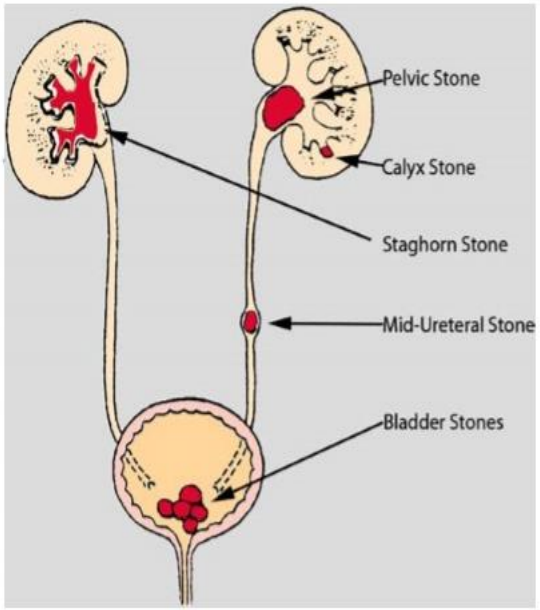

Figure No. 2: Location of staghorn and non-staghorn kidney stones. Staghorn stones fill various amounts of the renal collection system. Nonstaghorn stones can be very variable in size and can be found in a major or minor calyx, in the renal pelvis or at different sites along the ureters (proximal, middle or distal). Stones can also be found in the urinary bladder [16].

Classification of kidney stones:

There are different kinds of renal stones and their correct identification is important in the selection of optimal treatment. The frequency of different stone type occurrence is shown in Table 1[2]. Based on variations in mineral composition and pathogenesis, kidney stones are commonly classified into five types as follows [1].

Table No. 1: Classification of stones[17] :

Composition	Causative	Factors Frequency (%)
Calcium oxalate, phosphate, or both	Underlying metabolic abnormality Idiopathic (25%)	60-80
Struvite (triple phosphate)	Infection	10-15
Uric acid	Hyperuricaemia and hyperuricosuria Idiopathic (50%)	5-10
Cystine	Renal tubular defect	1
Other (xanthine, indigo, triamterene, indinavir*, etc)		1

*Pure uric acid and indinavir stones are radiolucent. Cystine stones are radio-opaque because of the sulphur content [17].

➢ Calcium Stones: Calcium Oxalate and Calcium Phosphate. Calcium stones are predominant renal stones comprising about 80% of all urinary calculi [1]. Urinary calcium could be kept within a satisfactory range with diet and drugs. The increase in urinary oxalate could be averted by dietary oxalate restriction. Urinary saturation of calcium oxalate dramatically decreased and new stone formation was virtually eliminated [3]. A reduction in urine oxalate reduces the supersaturation of calcium oxalate. In patients with the common form of nephrolithiasis, avoiding high-dose vitamin C supplements is the only known strategy that reduces endogenous oxalate production [2]. Calcium oxalate stones, which are the most common composition of kidney stones in patients with MetS, are reported to be affected little by any MetS trait [6]. The effects of inhibitors of stone formation have been primarily studied in calcium oxalate stones. Most inhibitors are anionic and seem to exert their effects by binding to the calcium oxalate surface, although the specific structural mechanisms of this process are not completely known [9]. Calcium oxalate kidney stones are produced in rats by the induction of acute or chronic hyperoxaluria using a variety of agents

such as sodium oxalate, ammonium oxalate, hydroxy-L-proline, ethylene glycol, and glycolic acid [14]. Calcium oxalate is a Ca salt of a dicarboxylic acid and oxalic acid, and it crystallizes into two different chemical and crystallographic forms, namely, calcium oxalate monohydrate (i.e. whewellite, $CaC_2O_4 \cdot H_2O$) and calcium oxalate dihydrate (i.e. weddellite, $CaC_2O_4 \cdot 2H_2O$). All Ca stones are radiopaque[9]. Urinary pH of 5.0 to 6.5 promotes Calcium oxalate stones, whereas calcium phosphate stones occur when pH is greater than7.5[1]. an alkaline urine pH promotes the formation of calcium phosphate-containing stones[6]. Calcium phosphate stones share the same risk factors as with calcium oxalate stones like higher concentrations of urine calcium and lower concentrations of urine citrate[2]. High sodium intake increases the potential risk for kidney stone formation by elevating urinary saturation of calcium phosphate and decreasing the inhibitor activity against calcium oxalate crystallization by lowering the urinary citrate excreation[13]. A magnesium-deficient diet also induces Calcium phosphate nephrolithiasis[14]. The uncomplicated calcium-stone disease can then be separated into hypercalciuric and normocalciuric groups [18].

➢ Struvite or Magnesium Ammonium Phosphate Stones: Struvite stones occur to the extent of 10–15% and have also been referred to as infection stones and triple phosphate stones [1]. These stones require complete removal by a urologist. The new stone formation can be avoided by the prevention of UTIs [2]. Admixed struvite/apatite stones are usually light brown with a coarse, granular surface. The interior of these stones is normally intermixed with white and light-brown layers. Struvite stones develop if alkaline urine, which has a raised concentration of ammonium, contains trivalent phosphate and urease produced by bacteria [9]. Urinary infection with urea splitting organisms (Proteus, Klebsiella, Pseudomonas, Corynebacterium species, Serratia, and Mycoplasma) creates alkaline urine that promotes the formation of struvite stones[12][17].

➢ Uric Acid Stones or Urate: This accounts approximately for 5–10% of all stone types. Diets high in purines especially those containing animal protein diets such as meat and fish results in hyperuricosuria, low urine volume, and low urinary pH (pH<5.05) exacerbates uric acid stone formation [1]. Increased excretion of urinary uric acid, sodium, calcium, and citrate in obese stone formers, along with an increased incidence of symptomatic uric acid stones [6]. Uric acid stones are radiographically transparent unless mixed with Ca crystals or struvite and, in contrast to the radiopaque Ca stones, they are radiolucent. Uric acid salts out calcium oxalate and can precipitate out in acid urine even in the absence of raised serum or urinary

uric acid concentrations. As with all stones, certain drugs may enhance stone formation, and in the case of uric acid stones, such drugs include hyperuricosuria agents, such as low-dose salicylates, probenecid and thiazides [9]. Hyperuricosuria —this not only contributes to uric-acid stone formation but also the formation of calcium oxalate stones [18]. UA stones are not easily seen on kidney, ureter, or bladder x-rays. On CT images, they resemble calcium stones, from which they can be distinguished by their lower density on I V. pyelogram radiograph, UA stones appear as filling defects [19]. Uric acid stones are more common in men than in women [1].

➢ Cystine stones: These stones comprise less than 2% of all stone types. It is a genetic disorder of the transport of amino acid and cystine. It results in an excess of cystinuria in urinary excretions [1]. The formation of cystine stones is the only clinical expression of cystinuria, and these are associated with a genetically determined defect in the renal transport of certain amino acids, including cysteine. Pure L-cystine stones are homogeneously composed of very small yellow spheroids [9]. Cystinuria (cystine stones) is an autosomal recessive trait, with an inborn error in the transport of dicarboxylic acids—cystine, ornithine, lysine, and arginine, commonly known as "COLA." The low solubility of cystine results in its precipitation and stone formation [17]. Cystine solubility is pH-dependent, with a modest increase if pH rises to 7·5, and a steeper increase with a pH above 7·5. The solubility of cystine in individual urine samples varies, owing to the solubilizing action of electrolytes and macromolecules [18].

➢ Drug-Induced Stones: This accounts for about 1% of all stone types [1]. Drugs such as guaifenesin, nelfinavir, oxypurinol, triamterene, atazanavir, and sulfa drugs induce these stones. For instance, people who take the protease inhibitor indinavir sulfate, a drug used to treat HIV infection, are at risk of developing kidney stones [28]. Such lithogenic drugs or its metabolites may deposit to form a nidus or on renal calculi already present. On the other hand, these drugs may induce the formation of calculi through its metabolic action by interfering with calcium oxalate or purine metabolism [29].

Kidney Stone Composition:

The chemical compositions of urinary stones include crystals and non-crystalline phases of the organic material (the matrix). The organic matrix of urinary stones consists of macromolecules such as glycosaminoglycans (GAG'S), lipids, carbohydrates, and proteins.

These molecules play a significant role by promoting or inhibiting the processes of kidney stone development. The main components of the stone matrix are proteins (64%), nonamino sugars (9.6%), hexosamine as glucosamine (5%), water (10%), and inorganic ash (10.4%) [1]. Renal calculi are crystalline structures composed most commonly of calcium oxalate salts. They form when the concentrations of these ions, as well as solutes such as hydrogen ions, sodium ions, and uric acid, are present in the filtrate in higher than normal amounts. This condition is known as supersaturation and supersaturated ions are more likely to come out of solution and crystallize [26].

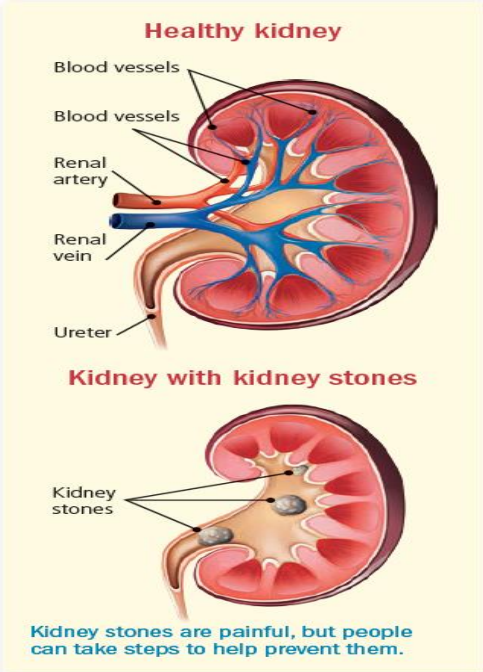

Figure No. 3: healthy kidney and kidney with kidney stones[30].

Symptoms of renal calculi:

- Discomfort in the side and back and below the ribs. This discomfort usually occurs only on the side of the renal calculi and does not cross over to the other side.
- Fluctuations in discomfort intensity, with periods of discomfort lasting 20-60 min.
- Discomfort waves radiating from the side and back to the lower abdomen and groin
- Bloody, cloudy or foul-smelling urine
- Discomfort, pain, and inflammation on urination

- Nausea and vomiting
- Persistent urge to urinate
- Fever and chills if an infection is present.

Mechanisms of Renal Stone Formation:

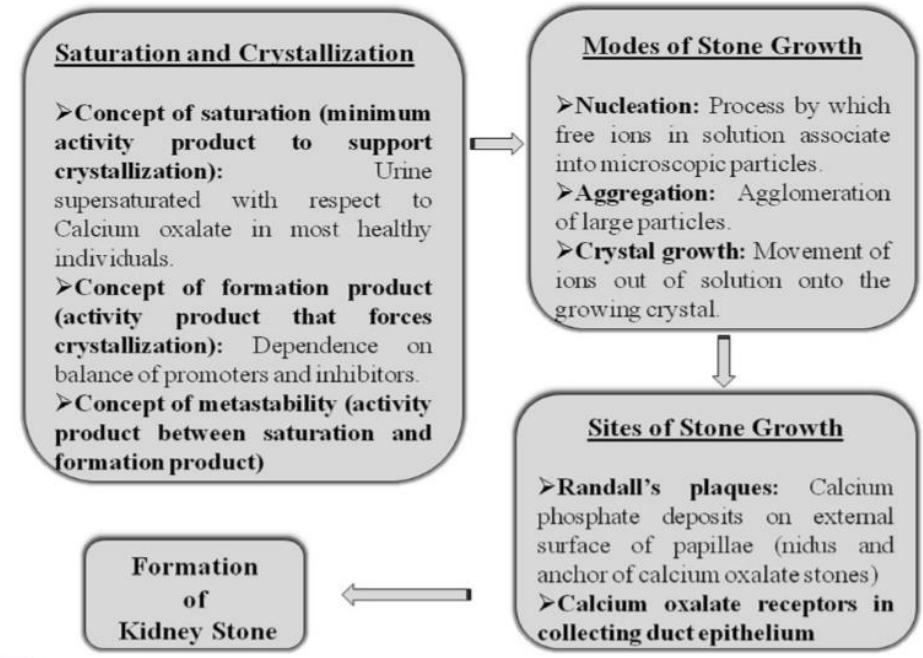

Figure No. 4: Multistep physiochemical processes and mechanism of kidney stone formation [9].

Renal stone formation is a biological process that involves physicochemical changes and supersaturation of urine. Supersaturated solution refers to a solution that contains more of the dissolved material than could be dissolved by the solvent under normal circumstances. As a result of supersaturation, solutes precipitate in urine leads to nucleation and then crystal concretions are formed. That is, crystallization occurs when the concentration of two ions exceeds their saturation point in the solution [1]. Three general pathways for kidney stone formation are seen: (1) stones fixed to the surface of a renal papilla at sites of interstitial apatite plaque (termed Randall's plaque), as seen in idiopathic calcium oxalate stone formers; (2) stones attached to plugs protruding from the openings of ducts of Bellini, as seen in hyperoxaluria and distal tubular acidosis; and (3) stones forming in free solution in the renal collection system, as in cystinuria. The presence of hydroxyapatite crystals in either the interstitial or tubule compartment (or sometimes both) of the renal medulla in stone formers

is the rule and has implications for the initial steps of stone formation and the potential for renal injury [16]. Randall (1936) was the first to describe the appearance of what is now known as "Randall's plaques", and although important aspects of the process of stone formation in humans have been explored over the years [9]. The plaque has been noticed for seven decades at least. Using modern digital imaging endoscopes one readily finds stones growing on plaque [15]. Reactive Oxygen Species (ROS) also promote cell membrane damage unmasking additional crystal binding sites, attached crystals form centers for nucleation of new crystals favoring stone development. Crystals up taken by endocytosis exacerbate cell damage. Alternatively, crystals may dissolve within lysosomes or re-emerge at the basolateral surface, again providing centers for stone growth in the renal interstitium. Cell death produced by oxalate exposure may leave cellular debris that forms a nidus for additional crystal growth, also promoting stone formation [26].

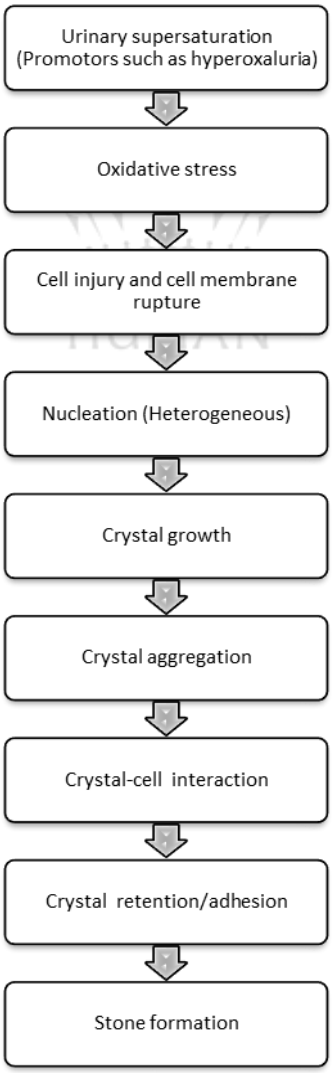

Figure No. 5: Schematic representation of the various events of kidney stone formation [1].

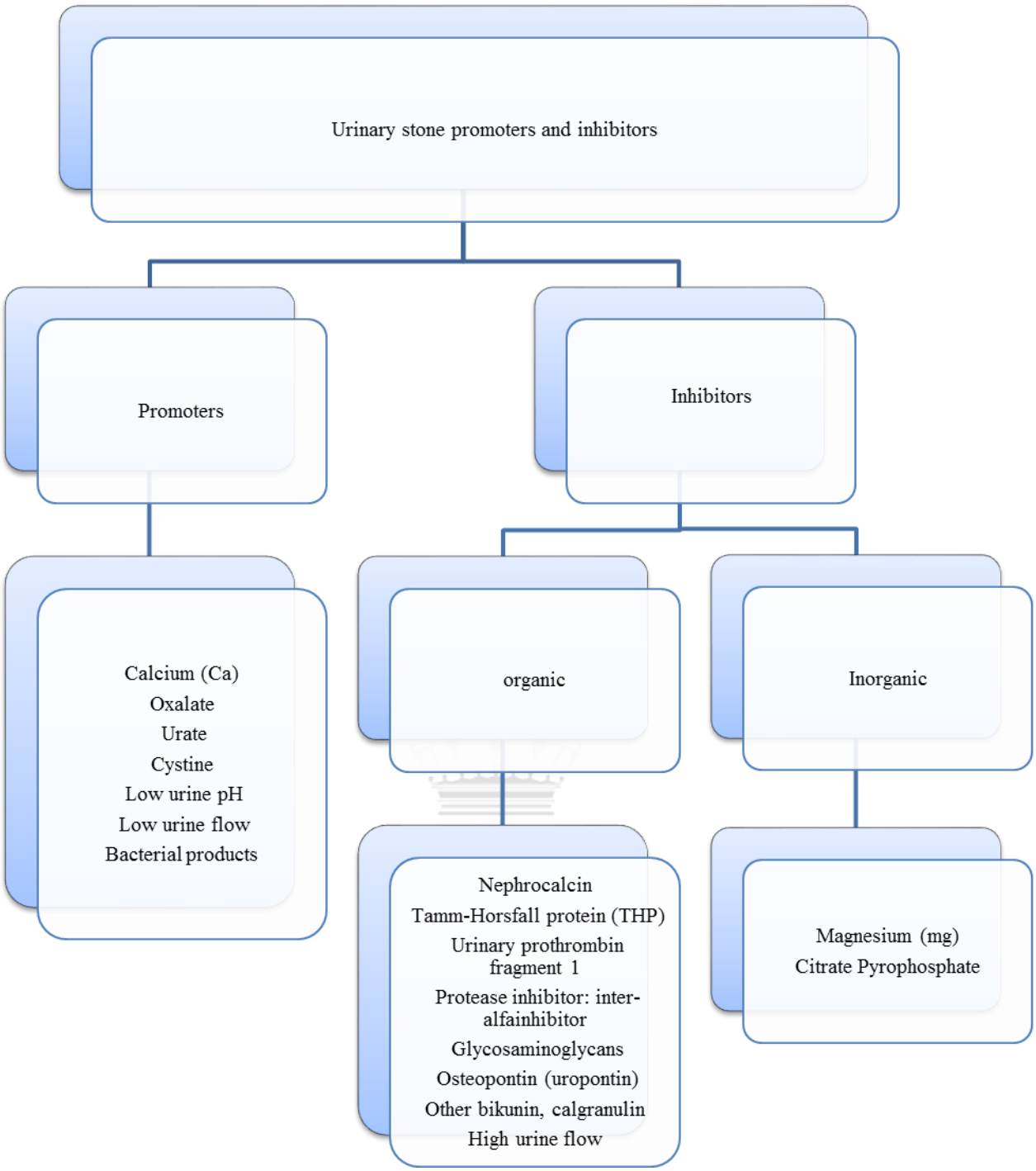

Figure No. 6: Urinary stone promoters and inhibitors [9].

Management:

Treatment of renal colic in the emergency setup involves I .v. fluids, analgesics and anti-emetic medication, and anti-emetic medication. When the diagnosis of renal colic is established, the presence of obstruction or infection should be determined [2]. Several guidelines are available to provide a clinical framework for diagnosis, follow-up, and

prevention of kidney stone disease. Metabolic screening is an important part of investigating kidney stone disease [6]. Complete management means not only proper evaluation and treatment, but also prophylaxis to prevent a recurrence, which is impossible without the knowledge of the composition of the offending stone [10]. Management of a kidney stone depends on its size, location, and composition and the presence of anatomical malformation and complications. The presence of a complication (complicated stone) infection or obstruction may necessitate immediate intervention, whereas uncomplicated stones can be managed conservatively with adequate fluid intake and analgesia [17]. Conservative treatment for hypercalciuric individuals with normal bone density includes a high fluid intake to ensure a minimum urine volume of 2 L/day, dietary sodium restriction (about 100 meq/day), oxalate restriction (avoidance of dark roughage, tea, nuts), increased citrus-fruit intake, avoidance of a meat-rich diet, and a moderate intake of dietary calcium (up to an equivalent of one glass of milk per day) [18]. Management of Calcium phosphate is usually treated with fluids and thiazide diuretics to lower urine calcium excretion. Urine citrate excretion can be reduced, as in idiopathic Calcium oxalate, but because potassium citrate salts can increase urine pH and Calcium phosphate SS, careful follow-up is needed. No clinical trials have documented treatment outcomes for Calcium phosphate [19]. The proper approach to diagnosis and management in patients with the first episode of a calcium-containing renal stone remains controversial. Watchful waiting might seem appropriate if predisposing conditions such as primary hyperparathyroidism and renal tubular acidosis have been ruled out, but at least two authorities have advised detailed diagnostic evaluation and long-term specific therapy in all patients [23]. Experience at many centers during the last few years has established that methods for percutaneous stone removal are practical and preferential for the treatment of surgical stone disease [22].

Preventive Options for Urolithiasis:

Effective kidney stone prevention depends upon addressing the cause of stone formation. Generally, to prevent the first episodes of kidney stone formation or its secondary episodes, proper management of diet and the use of medications is required. Primary prevention of kidney stone disease via dietary intervention is a low-cost public health initiative with massive societal implications. Thus, nutritional management is the best preventive strategy against urolithiasis[1]. Without medical treatment, the 5-year recurrence rate is high, ranging from 35–50% after an initial stone event. A high fluid intake, enough to produce at least 2.5 L

of urine per day, should be the initial therapy to prevent stone recurrence [2]. There is currently no treatment that satisfactorily meets the aforementioned criteria. Dietary calcium restriction seldom brings about satisfactory control of hypercalciuria in type I absorptive hypercalciuria especially in an ambulatory setting with nonconstant metabolic diets [3]. Decreased dietary salt consumption has been recommended in all patients with urinary stones, particularly those with hypercalciuria, and a prospective, randomized trial has demonstrated decreased stone formation during a 5- year period in a patient with idiopathic hypercalciuria who was on a low salt diet [4]. Several pharmacotherapies are available to prevent stone formation in patients with MetS, but lifestyle changes, in particular, dietary and exercise interventions, must not be forgotten as a therapeutic intervention for the prevention of both formation and recurrence of kidney stones. Such changes may not only help in the prevention of kidney stones but also in preventing and treating obesity, hypertension, coronary artery disease, as well as the MetS itself [6]. Worldwide epidemiological data show an increase in prevalence and incidence rates. In Germany, for instance, the incidence rate rose during the last decade from 0.54 to 1.47%. In the US, an increase of 37% in the stone disease was observed over the last 20 years. The reasons are multifold: lifestyle, dietary habits, and improved medical supply[11]. Decrease intake of animal protein (≤52 g/day) Reduces production of metabolic acids, resulting in a lower level of acid-induced calcium excretion; increases excretion of citrate that forms a soluble complex with calcium and reduces supersaturation concerning calcium oxalate and limits the excretion of uric acid [17]. Patients with kidney stones may warrant more aggressive screening for subclinical chronic kidney disease, and, if identified, measures to ameliorate progression may be important (e.g., angiotensin blockade). It is also possible that aggressive medical treatment to prevent recurrent kidney stones may decrease the risk for chronic kidney disease [24].according to the most recent national health and nutrition examination survey, the overall prevalence of self-reported kidney stones from 2007-2010 was 8.8%, with a higher prevalence among men(10.6%) than women(7.1%)[25].

Risk factors:

Epidemiological risk factors for urinary stone disease include patient age, gender, occupation, genetics, social status, geographic location, climate, and diet. Dietary modifications may decrease recurrent urinary stone formation [4]. The modern western lifestyle provides a host of factors that impair urine composition and thereby increase the risk of stone formation. In our

everyday life, we do not drink enough water and only twice or thrice a day, we eat food that is too rich in calories and table salt, but has deficiencies in fiber and alkali. Last but not least, we do not exercise enough. Recent work showed that being overweight is a crucial risk factor with a significant impact on stone formation [11]. High urinary sodium from salt abuse is a well recognized environmental or nutritional risk factor for kidney stone formation [13]. Overall, a high calcium intake probably does not carry an increased risk of stones in normal individuals and patients without absorptive hypercalciuria. However, a high calcium intake probably increases the risk of stones in patients with absorptive hypercalciuria [18]. Kidney stone formation is usually due to genetic and environmental factors. Although genetic factors influence stone risk, changes in the gene pool occur at a slow rate. Therefore, it is unlikely to be the driving force for these trends. Environmental factors are also varied and complex, but their influence is more apparent as changes in these factors occur over much shorter intervals [20]. Fluid consumption changes in fluid intake help prevent kidney stones. Drinking enough fluids each day is the best way to prevent most types of kidney stones by keeping urine diluted and flushing away materials that might form stones [26].

Important factors to identify in the patient's history

- **Presence of systemic illness-**

• Primary hyperparathyroidism • Renal tubular acidosis • Cystinuria • Gout • Diabetes mellitus • Inflammatory bowel disease • Renal insufficiency • Sarcoidosis • Medullary sponge kidney

- **Anatomical features-**

• Presence of horseshoe kidney • Previous urinary diversion • Obstruction of the ureteropelvic junction • Solitary kidney • Previous renal or ureteral surgery

- **Previous kidney disease-**

• History of urinary tract infection or pyelonephritis, or both •Family history of urolithiasis • Detailed history of previous stone events Treatment Stone analysis [21].

- **Drugs that may increase the risk of stone disease-**

• Decongestants: ephedrine, guaifenesin,

• Diuretics: triamterene,

• Protease inhibitors: indinavir,

• Anticonvulsants: felbamate, topiramate, and zonisamide,

*The non-dissolving carrier of osmotically controlled release oral (OROS) drugs may be misdiagnosed as kidney stones on x-ray [17].

Table no 2: Factors causing an increased risk of renal stone [2].

Factor	Example
Metabolic	High urine calcium
	High urine oxalate
	Low urine citrate
	Low urine Volume
Dietary	Low fluid intake
	Low calcium intake
	High intake of animal protein
	High oxalate intake
Infections	Recurrent urinary tract infection
Hereditary	Positive family history
Congenital anatomic defects	Medullary sponge kidney, horseshoe kidney, and ureteropelvic junction obstruction
Environmental	Hot and arid climate. People working outdoors in hot weather have an increased risk of stone formation due to excessive fluid loss from sweating.
Systemic disorders	Hyperparathyroidism, diabetes mellitus, hyperuricemia, metabolic syndrome etc.

SUMMARY

The incidence of urolithiasis is increasing worldwide. Many aspects of renal stone formation remain unclear. However, certainly, renal cell injury, crystal retention, cell apoptosis, Randall's plaque, and associated stone inhibitors or promoters play important roles for kidney stone formation. The increasing incidence of renal stones is adding to the morbidity and huge

economic losses worldwide of this pathology. Dietary restriction of calcium did not increase urinary oxalate when oxalate intake was also restricted. Calcium restriction also did not produce bone loss when thiazide and potassium citrate were concurrently given. Topiramate is generally well tolerated, and serious adverse events are rare. Nonetheless, the present review indicates that its use is linked with metabolic acidosis, hypokalaemia, hyperuricemia, and renal stone promotion. Worldwide obesity has more than doubled since 1980 with more than 600 million obese patients in 2014. The association of obesity with kidney stone disease has recently started drawing attention. Kidney stone disease affects Quality of life in most patients with the most impact on bodily pain and general health domains. A large number of trace elements are essential for specific metabolic processes, temporarily stored and then excreted via the kidneys. This can result in the accidental incorporation of trace elements into urinary stones, but also affect crystal formation or change the properties of urinary stones. A close look at the diet is worthwhile as recent studies strongly indicate that a low intake of animal protein, as well as sodium chloride and a high intake of alkaline potassium, are the keys to efficient stone prevention. Few stone formers are medically evaluated and treated to prevent recurrent stones. Understanding the pathophysiology of this disorder is also necessary for the development of new therapeutic options or treatment. In India, though nephrolithiasis is a common prevalence disease pharmacotherapy is neglected emphasizing the need to develop highly effective drugs for the treatment of nephrolithiasis. Simple and reliable diagnostic protocols are available to differentiate various causes of stones. A range of drugs is now available to correct metabolic disturbances and to prevent recurrent stone formation.

REFERENCES

1. Tilahun Alelign and Beyene Petros: Review Article Kidney Stone Disease: An Update on Current Concepts, Hindawi Advances in Urology Volume 2018, Article ID 3068365.
2. Ramesh Aggarwal, Anshuman Srivastava, Sachin Kumar Jain, Ritika sud, rati Singh: renal stones: a clinical review, EMJ European medical journal, page no. 98-103.
3. Charles y. c. Pak, Howard j. heller, Margaret s. Pearle, Clarita v. odvina, john r. poindexter and Roy d. Peterson: prevention of stone formation and bone loss in absorptive hypercalciuria by combined dietary and pharmacological interventions: the journal of urology, Vol. 169, February 2003, page no. 465-469.
4. Marshal l. Stoller, Thomas chi, brian h. Eisner, gina Shami and Donald l. Gentle: Changes in urinary stone risk factors in hypocitraturic calcium oxalte stone formers treated with dietary sodium supplementation. The journal of urology, vol.181, March 2009, page no. 1140-1144.
5. Valentina G. Dell'Orto, Eva A. Belotti, Barbara Goeggel Simonetti,Giacomo D. Simonetti, Gian Paolo Ramelli, Mario G. Bianchetti & Sebastiano A. G. Lava: Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review: British Journal of Clinical Pharmacology, page no. 958-964.
6. Yee Wong, Paul Cook, Ph.D., Paul Roderick, Ph.D., and Bhaskar K. Somani: Metabolic syndrome and kidney stone disease: A Systematic Review of Literature: Journal of endourology, Volume 30, Number 3, March 2016, page no. 246-253.

7. Francesca New & Bhaskar K. Somani: A Complete World Literature Review of Quality of Life (QOL) in Patients with Kidney Stone Disease (KSD), 22 October 2016.
8. Yaw A. Nyame, MD, MBA, Shubha De, MD1, Carl Sarkissian, BSc(Eng), Robert Brown, MD, Ganesh Kartha, MD, MS, Paurush Babbar, MD, Manoj Monga, MD: Kidney stone models for in vitro lithotripsy research: A Comprehensive Review: Journal of Endourology.
9. Vivek K. Singh & Pradeep K. Rai: Kidney stone analysis techniques and the role of major and trace elements on their pathogenesis: a review: International Union for Pure and Applied Biophysics (IUPAB) and Springer-Verlag Berlin Heidelberg 2014.
10. Mohd s Ansari, Narmada p Gupta, Ashok k hemal, premnath n Dogra, amlesh Seth, monish aron and tej p Singh: Spectrum of stone composition: structural analysis of 1050 upper urinary tract calculi from northern IndiaInternational Journal of Urology (2005).
11. Michael Straub and Richard E. Hautmann: Developments in stone preventionUrolithiasis Research Group, Department of Urology and Pediatric Urology, University of Ulm, Prittwitzstrasse, Ulm, Germany, page no. 119-126.
12. Neva Ciftciogle, Mikael Bjorklund, kai kuorikoski, Kim Bergstrom, and E. Olavi Kajander: Nanobacteria: An infection cause for kidney stone formation: kisny international,ol. 56(1999) page no. 1893-1898.
13. Khashayar sakhaee, jean a. Harvey, Paulette k. Padalino, Peggy Whitson and Charliss y. C. Pak: The potential role of salt abuse on the risk for kidney stone formation: the journal of urology, vol. 150, August 1993, page no. 310-312.
14. S. R. Khan, World J Urol: Animal models of kidney stone formation: an analysis: (1997), page no. 236-243.
15. Fredric l. coe , Andrew p. Evan, elaine m. Worcester, James e. lingeman : three pathways for human kidney stone formation: Urol Res (2010), page no. 147-160.
16. Andrew P. Evan, Pediatr Nephrol (2010): Physiopathology and etiology of stone formation in the kidney and the urinary tract, page no. 831-841.
17. Malvinder S Parmar: Kidney stones, BMJ, volume 328, page no.1420–4.
18. Charles Y C Pak: Kidney stones, the lancet • vol 351 • June 13, 1998, page no.1797-1801.
19. Fredric L. Coe, Andrew Evan, Elaine Worcester: Kidney stone disease: The Journal of Clinical Investigation. 2005; vol.115(10), page no. 2598-2608.
20. Victoriano Romero, MD, Haluk Akpinar, MD, Dean G. Assimos, MD: Kidney Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors: reviews in urology, VOL. 12 NO. 2/3 2010, page no. e86-e96.
21. Nicole L Miller, James E Lingeman: Management of kidney stones, BMJ, 3 march 2007, volume 334, page no.468-72.
22. joseph w. Segura, Davide. Patterson, Andrew j. leroy, hugh j. Williams, jr., David m. Barrett, ralph c. Benson, jr., Gerald r. may and claire e. Bender: percutaneous removal of kidney stones: review of 1,000 cases, the journal of urology, Vol. 134, December, page no.1077-1081.
23. Uribarri, MD; Man S. Oh, MD; and Hugh J. Carroll, MD: diagnosis and treatment: The First Kidney Stone, Jaime, Annals of Internal Medicine, Volume 111, 15 December 1989, page no. :1006-1009.
24. Andrew D. Rule, Eric J. Bergstralh, L. Joseph Melton, III, Xujian Li, Amy L. Weaver and John C. Lieske: Kidney Stones and the Risk for Chronic Kidney Disease Clinical Journal of the American Society of Nephrology 4,2009, page no. 804–811.
25. : Margaret sur pearle, David s. Goldfarb, dean g. Assimos, Gary curhan, Cynthia j. Denu- Ciocca, brain r. Matlaga, Manoj Monga, Kristina lea Penniston, Glenn m. Preminger, Thomas m. T. Truk and James Robert white: Medical management of kidney stones: AUG guideline the journal of urology, Vol. 192, August 2014.
26. Atul sohgaura and papiya bigoniya: Review article a review on epidemiology and etiology of renal stone: American Journal of Drug Discovery and Development, vol. 7 (2),2017, page no.54-62.
27. Glenn m. Preminger: Urinary calculi (nephrolithiasis; stones; urolithiasis) MSD manual professional version.
28. C. Barbasa, A. Garciaa, L. Saavedreaa and M. Muros: Urinary analysis of nephrolithiasis markers: journal of chromatography B, vol.781, no.1-2, page no.433-455, 2002.
29. M. Dursun, A. Otunctemur, and E. Ozbek: Kidney stones and ceftriaxone: European medical journal of urology, vol.3, no.1, page no.68-74, 2015.

30. Available from: https://www.health.harvard.edu/a_to_z/kidney-stones-a-to-z, 13/01/2020.