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Nephrolithiasis – Most Debilitating Renal Disorder

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Abstract

Both metabolic and environmental risk factors are involved in the pathogenetic mechanisms of kidney stone formation. Major advances have been made in the concept of the pathogenesis, diagnosis, and treatment of kidney stone disease over the last decade. It remains a major health burden worldwide. It is considered a systemic disorder associated with chronic kidney disease, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus, and the metabolic syndrome. Many therapeutic interventions which can effectively target the stones are available but these are associated with untoward effects. In the pursuit of finding better alternatives, large number of plants was screened for their antiurolithiatic activity. They were found to possess potent activity with minimal/no side effects. Development of new therapeutic agents is possible by understanding the link between nephrolithiasis and these systemic disorders.

***Keywords*:** *Nephrolithiasis, Calcium oxalate, Cystinuria, Nucleation, Crystal cell interaction*

INTRODUCTION

Nephrology is the scientific study of the anatomy, physiology, and pathology of the kidneys. After the kidneys filter blood plasma, they return most of the water and solutes to the blood stream. Urine is made with remaining water and solutes. It passes through the ureters, stored temporarily in the urinary bladder and then excreted out through the urethra. The branch of medicine that deals with the male and female urinary system and the male reproductive system is urology.

FUNCTIONS OF URINARY SYSTEM

The kidneys perform wide range of functions which include regulation of composition and volume of blood, blood pressure, synthesis of glucose and vitamin-D, release of erythropoietin and excrete wastes in the urine.

Being the vital excretory organ, kidneys are susceptible to various pathogenic stimuli leading to marked reduction in their function. The following are some of the most common renal problems:

LIST OF KIDNEY DISEASES

- Acute kidney failure or acute kidney injury
- Acute tubular necrosis
- Anorexia nervosa and kidney disease
- Congenital nephrotic syndrome
- Diabetes and diabetic kidney disease
- Diabetes insipidus
- Glomerular disease
- Good pasture syndrome
- Kidney stone, nephrolithiasis
- Lupus, systemic lupus erythematosus
- Medullar cystic kidney disease
- Metabolic acidosis
- Myeloproliferative neoplasms and glomerulopathy
- Nephrotic syndrome
- Neurogenic bladder
- Renal artery stenosis
- Urinary tract infection

Among the above mentioned renal disorders urolithiasis is the most common debilitating disorder.

NEPHROLITHIASIS OR UROLITHIASIS

Chemicals present in the urine usually results in the formation of kidney stone. Various wastes are present in the urine. Crystals begin to form when the amount of these wastes increases. Other elements deposit on these crystals to form a solid that will not get excreted if its size is larger. Kidneys usually eliminate these chemicals through the urine. Consumption of more liquid helps to remove the wastes and stops the formation of stones. The stone may stay either in kidney, urinary tract or ureter after its formation. If the stone size is small then it passes out without causing much pain. But stones that don't move may cause a backup of urine in the kidney, ureter, the bladder or the urethra. This is what causes the pain. Clinically, this condition is referred to as "NEPHROLITHIASIS"[1].

TYPES

There are four types of kidney stones which blocks and alters the kidney functions [2, 3]. They are as follows:

CALCIUM STONES/IDIOPATHIC HYPER CALCIURIA

They are more common in urea. The average age of onset is the third decade, approximately 60% of people who form a single calcium stone eventually form another within the next 10years. The average rate of new stone formation in patients who have had a previous stone is about one stone every 2or3 years. Calcium stone disease is frequently familiar. In the urine, calcium oxalate monohydrate crystals (whewellite) usually grow as biconcave ovals that resemble red blood cells in shape and size but may occur in a larger, "dumbbell" form. In polarized light the crystals appear bright against dark background with an intensity that is dependent on orientation, property known as birefringence, Calcium oxalate dihydrate crystals (weddelite) are bipyramidal [4]. This condition appears to be hereditary and its diagnosis is straight forward. In some patients, primary intestinal hyper absorption of calcium causes transient postprandial hypercalcemia that suppresses secretion of parathyroid hormone. The renal tubules are deprived of the normal stimulus to reabsorb calcium at the same time that the filtered load of calcium is increased. In other patients, reabsorption of calcium by the renal tubules appear to be defective and secondary parathyroidism is evoked by urinary losses of calcium. Renal synthesis of 1, 2,5dihydroxyvit-D is increased, enhancing intestinal absorption of calcium [5]. In the past the separation of absorption and renal forms of hyper calciuria was used to guide treatment. Hypercalciuria contributes to stone formation by raising urine saturation with respect to calcium oxalate and calcium phosphate [6].

URIC ACID STONES

They are radiolucent and are also more common in urea. Half of the patients with uric acid stones have gout. Uric acid lithiasis is usually familiar whether or not gout is present. In urine uric acid crystals are red-orange in colour because they absorb the pigment uricine. Anhydrous uric acid produces small crystals that appear amorphous by light microscopy. They are indistinguishable from apatite crystals, except for their birefringence. Uric acid dihydrate tends to form tear drop-shaped crystals as well as flat, rhomboid plates. Uric acid granules appear like red dust [7]. These are formed because the urine becomes supersaturated with undissociated uric acid that is protonated at its N-9 position. In gout, idiopathic lithiasis and dehydration, the average pH is usually below5.4 and often below5.0 undissociated uric acid therefore predominates and is soluble in urine only in concentration of 100mg/L. Concentration above this level represents super saturation that causes crystals and stone formation. Uric acid crystals can cause acute renal failure.

CYSTINE STONES

These are uncommon, lemon yellow and sparkle. Radiopacity is due to the sulfur content; they are in flat, hexagonal shapes. In this, proximal tubular and jejunal transport of the dibasic amino acids cystine, lysine, argenine and ornithine are defective and excessive amounts are lost in the urine. Cystine is transported by a separate transport mechanism because cystinuria and dibasic amino aciduria can occur independently [8]. Three types of inheritance have been described. A gene located on chromosome 2 and designated SLC3A1, codes for a dibasic amino acids transporter and has to be formed to be abnormal in type1 cystinuria. Linkage analysis has mapped type3 cystinuria chromosome19.

STRUVITE STONES

These are common and potentially dangerous. These stones occur mainly in women or patients who require chronic bladder catheterization and result from urinary tract infection with urease producing bacteria, usually proteus species. The stones can grow to larger size and fill the renal pelvis and calyces to produce a "staghorn" appearance. They are radiopaque and have a variable internal density. In urine, Struvite crystals are “rectangular prisms” said to resemble coffin lids [9].

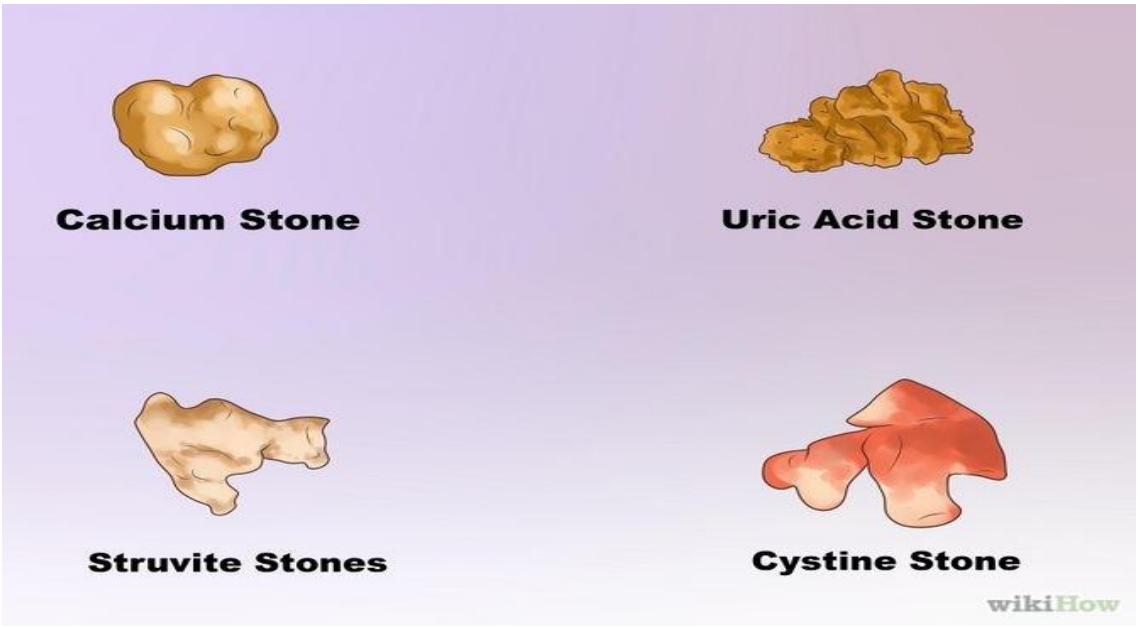

Figure 1: *Types of stones*

PREVALENCE

The prevalence of urolithiasis is approximately 2-3% in the general population, and the estimated life time risk of developing a kidney stone is about 10% for white males. Approximately 50% of patients with previous urinary calculi have a recurrences within 10years. Stone disease is 2-3times more common in males than in females [10]. It occurs more often in elderly persons of Asians ethnicity, who is affected more often than blacks.

CAUSES OF KIDNEY STONES

The risk of developing kidney stones could increase by calcium and vitamin-D supplements because they elevate calcium levels in the blood and urine. Chemically kidney stones are calcium oxalate, formed due to the precipitation of dissolved minerals on the inner lining of kidneys. These deposits can grow to the size of a golf ball while maintaining a sharp, crystalline structure [11].

Lack of water is the important cause of kidney stones. Stones commonly have

been found in these that drink less than the recommended eight to ten glasses of water a day. The pH level in the kidneys decreases and becomes more acidic when there is inadequate water to dilute the uric acid. An excessively acidic environment in the kidneys is conductive to the formation of kidney stones. Medical conditions such as crohn's disease, urinary tract infections renal tubular acidosis, hyper parathyroid, medullary sponge kidney, and dent's disease have been known to lead to kidney stones. Addition of fluoride to drinking water (fluoridation) has been suggested to be responsible for some cases of kidney stones. Magnesium ammonium phosphate stones are formed largely after infections by urea splitting bacteria (ex: proteus and some staphylococci) which convert urea to ammonia. Magnesium ammonium phosphate salts precipitate due to the alkalization of urine.

More than half of all patients with urate calculi have neither hyperuricemia nor increased urinary excretion of uric acid [12].

COMPLICATIONS OF KIDNEY STONES

If a kidney stone is blocking your ureters, you may develop a severe infection, which can become life threatening without treatment. Signs of an infection include having a fever and cloudy urine [13]. It's essential to take treatment in the presence of these symptoms. People suffering with recurring kidney stones are thought to have

- A 20% chance of having another within 5 years.
- A 35% chance of having another within 10 years.
- A 75% chance of having another within 20 years.

The best way to help prevent recuring kidney stone is to drink plenty of water every day to avoid dehydration.

SYMPTOMS OF THE KIDNEY STONES

A kidney stone usually remains symptomless until it moves into the ureter. When symptoms of kidney stone become apparent, they commonly include.

- Severe pain in the groin and/or side
- Blood in urine
- Vomiting and nausea, feeling sick
- WBC or pus in the urine
- Reduced amount of excreted urine
- Burning sensation during urination
- Persistent urge to urinate
- Fever and chills if there is an infection
- Sudden spasms excruciating pain these usually starts in your back below your ribs and move down and around to the front of your abdomen(tummy)
- The pain may wake up you when you are asleep and, may last between three and 18hours. [13].

MECHANISM OF RENAL STONE FORMATION

Urinary supersaturation and formation of crystalline particles lead to the development of renal stones. Super saturation is the driving force for crystallization in solution like urine [14]. Until a particular concentration, the salt or solute gets dissolve in the solvent after which no further dissolution is possible. Then the solvent is said to be saturated with the salt. The salt gets crystallizes out if added more in the constant temperature and pH. The concentration at which this crystallization begins is termed as thermodynamic solubility product (Ksp). It finally results in nephrolithiasis if inhibitors were not able to act. These inhibitors permit to hold higher amount of calcium in solution rather than pure solvent. Urine is metastable with respect to calcium salts. Indeed, stone formers tend to excrete that is more supersaturated than that of non stone formers [15]. It has been suggested that with a transit time across kidney of 5-10 min, residence time is too short for crystals to nucleate and grow

large enough to be trapped in a normal person.

CRYSTAL NUCLEATION

Conversion from a liquid to a solid phase in a supersaturated solution is termed nucleation which is the first step involved in kidney stone formation. It starts by the binding of salts in solution to form loose clusters which increase in size by addition of new clusters [16].

The first crystals formed from the nuclei do not dissolve and possess a characteristic lattice pattern. This process of formation of crystals from nuclei is called as heterogenous nucleation. In urine, epithelial cells, urinary casts, RBCs and other crystals act as nucleating centers. The saturation necessary for this heterogenous nucleation is much less than that of homogenous nucleation [17]. Once the anchoring of the generated nucleus occurs, crystallization process proceeds at relatively lower chemical pressure than required for the formation of initial nucleus. Renal tubular cell injury can promote crystallization of CaOX crystals by providing substances for their heterogenous nucleation. *In*-vitro cell degeneration following renal tubular cell injury produces numerous membrane vesicles, which have been shown to be good nucleators of calcium crystals. In vitro crystals observed in the renal tubules of hyperoxaluric rats are always associated with cell degeneration products.

CRYSTAL GROWTH

Once a crystal nucleus has achieved a critical size and relative super saturation remains above one the overall free energy is decreased by adding new crystal components to the nucleus, this process is called the crystal growth. Crystal growth is one of the prerequisite for particle formation and thus for stone formation, crystal growth and aggregation have important functions. Honda et al reported that the crystal surface binding substances which is found in CaOX crystals generated from whole human urine is strong inhibitors of CaOX crystal growth and contains proteins like human serum albumin, retinol binding protein, transferring, Tamm-horsfall glycoprotein and prothrombin [18]. The importance of crystal growth for the most abundant stone ie., CaOX is questionable. The probability of single particle is extremely low because the rate of CaOX crystal growth is low and transit time of tubular fluid through the kidney is several minutes [19]. Achieving pathophysiologic ally relevant size by the process of crystal growth alone is extremely low, even if growth proceeds at an uninhabited rate of 2mm per minute. Based on the quantity normally excreted, the inhibitory effect of fibronectin (FN) on the growth of CaOX crystals is small.

CRYSTAL AGGREGATION

Aggregation is the process of binding of crystals in solution to form larger particles. It is the most important step in stone formation according to some researchers. The process of crystal growth is very slow that it cannot become large enough to obstruct the renal tubules and retained there by this mechanism alone. Hence the crystal aggregation is considered to be the critical step in stone formation [20]. According to all models of CaOX urolithiasis, crystal aggregation is probably involved in the retention of crystals in the kidney. It has a prominent effect on particle size and aggregated crystal are commonly found in urine and renal stones. Viscous binding promotes crystal aggregation indicating that foreign compounds with multiple binding sites such as Tamm-Horsfall glycoprotein attach to crystal surface and act as kind of glue [21].

CRYSTAL CELL INTERACTION

The mechanism of crystal cell interaction is thought to be very complex, and many of them remain unexplored. Crystallization is caused by the condition of urinary super

saturation. Then, the crystals that have formed attach to renal tubular epithelial cells and are taken into them. The process of attachment or endocytosis of crystals to renal tubular cells, what is generally meant by crystal cell interaction these structural and functional studies of crystal cell interaction in culture indicate that calcium oxalate monohydrate (COM) crystals rapidly adhere to microvilli or the cell of surface and are subsequently internalizes [22]. Khan et al. concluded that urinary stone disease develops due to interaction of crystal cells. It is thought to be the first process in the formation of kidney stones. According to Finlayson and Reid hypothesis, it was unlikely to block renal tubules by the growth of CaOX crystals, and that attachment of crystals was necessary for initiation of stone formation. There have been many reports on crystal attachment. Animal model and tissue culture studies have provided evidence for crystal retention within the kidneys via attachment to renal epithelial cells crystal attachment to the brush border of proximal tubules in rats. Experimental introduction of CaOX urolithiasis starts with hyperoxaluria followed by crystalluria and deposition in the kidney. Some urinary macromolecules have an inhibitory effect on CaOX crystal attachment. Diverse polyanionic molecules in urine, such as specific glycosaminoglycans, glycol proteins, and citrate, block the binding of COM crystal to the cell membrane [23]. One common feature of molecules that inhibit COM crystals and adhesion to cells is their polyionic character. They mentioned that although polyanions present in tubular fluids may coat crystals and thereby inhibit their adhesion to tubular cells, a distinct and separate set of signals act on the cells to regulate their response to crystals that to bind.

DIAGNOSIS AND INITIAL MANAGEMENT OF KIDNEYS

Urolithiasis is a challenging problem to clinicians since the time of Hippocrates and many physicians have good experience in its management. Technical advancements in recent years have facilitated the proper diagnosis of this disease. There is a gradual development in the management of urolithiasis. Clear indications for urologic refferralare based on recognition of the few urgent situations and a solid understanding of the natural history of stone progression [24].

Table 1: *Imaging Modalities in the Diagnosis of Ureteral Calculi*

Imaging modility	Sensitivity (%)	Specificity (%)	Advantages	Limitations
Ultrasonography	19	97	Accessible require no ionizing radiation	Poor visualization of ureteral stones
Pain radiography	45-59	71-77	Accessible and inexpensive	Stones in middle section of ureter, phleboliths, radiolucent calculi, non genitourinary conditions
Intravenous pyelography	64-87	92-94	Accessible provides information on anatomy and functioning of both kidneys	Variable quality imaging requires bowel preparation delayed images require in high grade obstruction
Noncontrast helical computed tomography	95-100	94-96	Most sensitive and specific radiologic test. An indirect sign of the degree of obstruction provides information on non genitourinary conditions.	Less accessible and relatively expensive no direct measure of renal function.

PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Urolithiasis should always be considered in the differential diagnosis of abdominal pain. The pain of renal colic often begins as vague flank pain. Patients frequently dismiss this pain until it evolves into waves of severe pain. It is believed that a stone must at least partially obstruct the ureter to cause pain. The pain is commonly referred to the lower abdomen and to the ipsilateral grain [25]. As the stone progresses down the ureter, the pain tends to migrate caudally and medially.

STONE LOCATION	COMMON SYMPTOMS
Kidney	vague flank pain, hematuria
Proximal ureter	renal colic, flank pain, upper abdominal pain
Middle section of ureter	renal coli, anterior abdominal pain, flank pain
Distal ureter	renal colic dysuria, urinary frequency, anterior Abdominal pain, flank pain

Urine analysis should be performed in all patients with suspected calculi. A side from the typical microhematuria, important findings to note is the urine pH and the presence of crystals, which may help to identify the stone composition [26]. Patients with uric acid stones usually present with acidic urine and those with stone formation resulting from infection have alkaline urine

Identification of bacteria is important in planning therapy and a urine culture should be routinely performed [27]. Limited pyuria is a fairly common response to irritation caused by a stone and in absence of bacteruria is not generally indicative of coexistent urinary tract infection [28, 29]. Urinary calculi can also be detected by modern imaging studies which provides exact location and severity of the situation (Table 1).

KIDNEY STONES MEDICATIONS MEDICINE TO HELP PASS STONES

Non-steroidal anti-inflammatory drugs (NSAIDs) may relieve pain while passing a stone [30]. Doctors may also prescribe medicine to pass the stone such as alpha-blocker

MEDICINES TO PREVENT STONES

Calcium stones: most common stones.

- Orthophosphate
- Potassium citrate
- Thiazides

Uric acid stones

- Allopurinal
- Potassium citrate
- Sodium bicarbonate

Cystine stones

- Penicillamine
- Potassium citrate
- Tiopronin

Struvite stones

- Urease inhibitors
- Antibiotic to cure the infection [31, 32]

Medical management of patients with urolithiasis is crucially important for their outcome. The principle goals of medical efforts are manifold as listed below.

- Relief pain during renal colic.
- From spontaneous expulsion of ureteral stones
- Prevent formation or growth of renal stones
- Reduce the need of urologic procedures
- Reduce the occurrence of complicating events such as infection and/or obstruction
- Prevent renal tissue injury

- Avoid onset and progression of renal insufficiency

Alternative or complimentary medicine

Now-a-days, however, herbal medicine has gained much popularity because, herbal medicines are more effective, have less side effects, and reduce recurrence rate of stone formation. Hence search for antilithiatic drug from natural sources has assumed greater importance and promising. Herbal medicines have many phytoconstituents which may exert their beneficial effect in kidney stone treatment. Many plants were screened for their antilithiatic activity and proved to be potent.

SURGERY FOR KIDNEY STONES:

Surgery may be needed to remove a kidney stone if it

- Causes pain without passing out even after a reasonable period of time.
- Caught in a different place because of its large size.
- Urine flow is blocked.
- Urinary tract infections are resulted.
- Damages kidney tissue or causes constant bleeding.
- Stones are seen in X-ray if grown larger.

Open surgery was necessary to remove a stone up to 20 years back. The surgery required a recovery time of 4 to 6 weeks [33]. Many options do not require major open surgery and can be performed in an outpatients setting.

COMPLICATIONS OF TREATMENT

The different kinds of treatment for larger stones may cause some complications. The surgeon should explain these procedures.

Possible complications will depend on type of treatment, the size and position of stones.

Complications could include.

- Sepsis- an infection that spreads through the blood, causing symptoms throughout its whole body.
- Steinstrasse- this is the medical name for a blockage caused by fragments of stone in the ureter.
- An injury to the ureter.
- Urinary tract infection.
- Bleeding during surgery.
- Pain.
- It is estimated that 5-9% of people may experience Complications after having Uretrorenoscopy [34].

PREVENTION

Rather than having to undergo treatment, it is best to avoid kidney stone in the first place when possible. It can be especially helpful to drink more water, since low fluid intake and dehydration are major rule factors for kidney stone formation [35].

People who have a tendency to form calcium oxalate kidney stones may be advised to limit their consumption of blood high in oxalate, such as spinach rhubarb, Swiss chord, beat, wheat grains and peanuts. Also drinking lemon juices or lemonade may be helpful to prevent kidney stones [36].

Over the counter pain medicines ibuprofen, naproxen either alone or along with narcotics can be very effective.

CONCLUSION

Nephrolithiasis, a systemic disorder that may progress into end-stage renal disease. Hence the term stone former is used. It is a pandemic disorder with increasing incidence as that of diabetes mellitus, metabolic syndrome and the aging population. The pathogenesis of nephrolithiasis is a complex mechanism that is not fully explored suggesting that kidney stones are phenotype of a syndrome in which genetic, environmental and metabolic factors each contribute to a different extent. Understanding the pathophysiological pathways of lithogenesis encourage physicians to treat

nephrolithiasis as part of this syndrome rather than as an isolated disease. Although many theories have been proposed and much research has been carried out, further investigation in this field is required.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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