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"KIDNEY STONE: A CLEAR REVIEW OF ETIOLOGY, PATHOPHYSIOLOGY AND FACTORS"

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ABSTRACT

Kidney stone is one of the most common urological disorders and one of the oldest diseases, which affects 10‑12% of the world population. Pathophysiology of the disease includes urine supersaturation which promotes nucleation and aggregation of crystal then crystal retention occurs in the epithelium of urinary tract leads formation and growth of stone. Lithiasis is a term used for formation of stone in the urinary tract system. Stone can be in range from "A grain of sand to a pearl" with some "as big as golf balls". Calcium containing calculi are the most common comprising about 80% of all urinary calculi, rest 20% are of other types. There are some promoters and inhibitors which have most important roll in the formation of calculi. They can cause excruciating pain or no symptoms at all. To determination of the presence of kidney stones, various imaging techniques were used now a day. Which is useful for proper knowledge about the location and type of calculi.

KEYWORDS: Kidney stone, Lithiasis, Pathophysiology, calculi.

INTRODUCTION

Kidney stone is a multifactorial disease and a complicated urinary disorder. Lithiasis is the condition where urinary calculi (stone) are formed in the kidneys and urinary tract[1] and Kidney stones, which are solid crystals that form from dissolved minerals in urine, can be caused by both environmental and metabolic problems. Kidney stones is also known as Urolithiasis (derived from the Greek words ouron (urine) and lithos (stone)[2], Nephrolithiasis[3], Renal lithiasis[4] and renal calculi.[5] Kidney stones increasingly have develop into recognized as a systemic disorder associated with diabetes mellitus,

hyperuricemia, obesity, hypertension, hypercholesterolemia and chronic kidney disease which can involve entire system of person.[6] Prevalence has doubled in just the last decade, rising from approximately 6%–11% among men and 4%–7% among women, respectively between 1994 and 2012.[7] In most of the patients, stones are unilateral (one-sided) but some have bilateral (two-sided). Nonobstructing stones produce no signs or symptoms apart from hematuria and if the stone obstructs the uretero-pelvic junction, pain localizes to the flank; as the stone moves down through the ureter, pain moves downward and anterior.[8]

Kidney stones may lead to swollen kidneys, infections of kidneys and finally to kidney failure. In a healthy persons, during the residence time of urine in the urinary tract system, crystals either do not form or are so small they are eliminated uneventfully (asymptomatic crystalluria). When normal urine conditions altered, then the rate of crystal nucleation and growth may become such that the crystals cannot be simply eliminated due to their large size. Crystal formation is attributable to a combination of diverse factors that may or may not be associated with an underlying disorder. These factors can be classified into two main groups: renal morphoanatomy factors and urine composition factors.[9]

There are two main renal morphoanatomy factors that can affect crystal formation.

a. The presence of cavities (formed by renal calices) with low urodynamic efficacies that retain urine for long periods

b. An altered epithelium covering the renal papillae, which can arise from events such as damage to the anti-adherent glycosaminoglycan layer that covers the uroepithelium, necrosis, or the presence of subepithelial calcifications.

Urine composition factors are important in crystal formation as urine is a metastable liquid containing several coexisting substances that can crystallize to generate renal calculi. These substances are present at supersaturated levels (the system contains higher amounts of solute than that corresponding to the solubility) meaning the urine is in an unstable state and a stable urine state will eventuate through crystallization of the excess solute. The ease of crystallization depends on the degree of supersaturation, the presence of preformed particles and the level of crystallization inhibitors. These latter substances inhibit crystal nucleation and/or growth.[10]

Etiology

Kidney stone often no definite, single cause, although there are various factors which is In 1993 Daudon *et al.* established the first classification of kidney stone with a clear correlation with the main urinary etiologic environment. However, this information is multifarious and probably is difficult to adapt responsible for formation of stone in the urinary tract and are made of salts and minerals in the urine that stick together to form small "pebbles". They may be as small as grains of sand or as large as a golf balls. Most stone are formed due to combination of genetic and environmental factors. In lithiasis, there are various factors of the urinary systems and the other diseased conditions that normally regulate orderly supersaturation and nucleation in the urine.

A. Dehydration

Person who has a kidney stone should drink adequate water and other fluids intake to produce at least 2 liters of urine a day which helps to decrease the concentration of substance (promoters of stone formation) involved in supersaturation thus reducing their supersaturation degree in the urine. Drinking enough fluid is the most important thing a person can do to prevent kidney stones.[11]

B. Overweight

It can cause both increased calcium in the urine and insulin resistance, which can result in a greater risk of lithiasis.[12]

C. Genetic factor

lithiasis is an inherited disease. If any people in your family have had kidney stone there is a chance, you have them too. In one analysis of lithiatic patients, 14% of their siblings and 22% of their parents had stone.[13]

D. Dietary factors

High intakes of beverages, calcium, oxalate, sodium, animal protein are the major dietary factors which increase the risk of stone formation.[14]

- Beverages like alcohol and caffeinated drinks i.e. cola, tea, coffee cause the kidney to excrete more water. If the person drink too much alcohol or caffeine and without enough water or other liquid, then the person become dehydrated which cause more minerals

concentration in urine and leads to stone formation. The subsequent stone may stay in the kidney or travel down the urinary tract.

- Too much calcium in the digestive tract binds to the oxalate (from food) and keep it from entering the circulatory system and then urinary tract, where it may nucleate and aggregate in the epithelium wall of the kidney then form stone.

- Some of the oxalate in urine is made by our own body. However, eating certain foods (green vegitables) and juice (apple and cranberry) contain high levels of oxalate can increase the level of oxalate in the urine, where it combines with calcium to form calcium oxalate stones. Similarly, grape fruit juice has been associated with increased risk of stone formation.

- A high salt (sodium chloride) intake has been shown to increase the amount of protein and excess more calcium into the urine. Protein is major risk factor for decline in the function of kidney where as high calcium level combine with oxalate and phosphorus to form calculi in the urinary system.

- Eating too much animal protein such as meat, eggs, poultry and see foods contain purines which break into uric acid in the urine which boosts the level of uric acid and leads to formation of calculi. Animal protein may also increase the risk of calcium stone by increasing the excretion of calcium and reduce the excretion of citrate (endogenous inhibitor) into the urine. Citrate prevents formation of stone in kidney but the acids in animal protein reduce the citrate in urine.

E. Disturbances in urinary pH

Both highly acidic urine (pH =5.5) and highly alkaline urine (pH = 6.7) predispose patients to calcium kidney stone formation. With unduly acidic pH, urine becomes supersaturated which leads the calculi formation.[15]

F. Associated disease: there are various disease which may direct or indirect related to the function of kidney or may change the electrolyte balance in the urinary tract system some of these are-

- **Primary hyperoxaluria**

It results from the over production of the oxalate. Oxalate is filtered by the kidneys and excretes as a waste product in the urine, leading to the high level of oxalate in urine after this oxalate bind with urinary calcium to form calcium oxalate (CaOx), a hard compound that is the main component of kidney and bladder stone.

- **Sarcoidosis**

Disturbed calcium metabolism is a feature of Sarcoidosis which is main cause of hypercalcaemia. The vitamin D_3 or its hormonally active metabolites, calcitriol (lα, 25-$(OH)_2D_3$) is a main cause for hypercalcaemia.[16]

- **Distal renal tubular acidosis (Type-I RTA)**

It can cause the dysfunction of kidney so the balance of electrolyte may change and cause high level of calcium in urine which result the stone in urinary system.[17]

- **Dent's disease**

It is the condition in which abnormally large amount of protein present in the urine (tubular proteinuria), hypercalciuria, calcium deposits in the kidney (nephrocalcinosis) which orderly results the stone formations.[18]

- **Crohn's disease**

This disease condition associated with hyperoxaluria and malabsorption of magnesium.[19]

- **Hyperparathyroidism:** the job of parathyroid gland is to control the amount of calcium in the circulatory system. When abnormalities occurs, can cause increase level of calcium in the blood so excretion of calcium is increased into the urine, which can cause development of stone in kidney.[20]

- **Medullary sponge kidney:** 8-20% of people who form calculi in kidneys have medullary sponge kidney.[21]

- **Gout:** The prevalence of renal calculi in gout patients was 13% and 2.7% of people with renal calculi had been found with gout, with the incident of gout being 8.6 percent in patients with 2 or more sequences of renal calculi.[22]

G. Hormones: sex hormones play a role in mechanism of renal calculi. Estrogen, testosterone and progesterone modulate the producing of lα, 25-$(OH)_2D_3$ which can leads calcium absorption in the kidney. Testosterone increases renal oxalate deposition and urinary oxalate excretion in castrated rats fed diets supplemented with glycolate. Males have the greater prevalence of kidney stones.[23]

H. Geographic differences

The incidence of lithiasis is greater in nations with hot or warm weather. In a population, calculi re-occurrence is greater in summer & spring than in winter & autumn season. Deficient low urinary output & intake of fluid are probably the major factors of greater incidence in warm countries.[24]

I. Medications

Loop diuretics cause elevated excretion of calcium, whereas phenytoin, sulphamethoxazole, triamterene, indinavir and acyclovir may precipitate as crystals for suitable situations. Antacids tie phosphate in intestine, resulting into elevated absorption and availability of calcium & influencing to calcium calculi. Vitamins D & A administered in excess can lead to hypercalciuria & hypercalcemia.[25]

Pathogenesis of Stone Formation

A Kidney stone or the urinary stone is formed when the normal balance of water, ions, salts, minerals and other components found changed in urine. It is a complex process, stones found in all parts of the urinary tract and kidney that leads to deficiency of different vitamins and hormones in the body. During this era, a lot of remedies have been employed for take care of kidney stones. On the one hand, kidney plays an important role in water conservation, but at the same time, minerals with low solubility need to be excreted. In general, there are different types of renal stone and each type of stone has its own group of cause. Levels of urinary supersaturation correlate with the type of stone formed and lowering supersaturation is effective for preventing stone recurrence.[26] Calcium oxalate (CaOx) is the predominant component of most stones accounting for more than 80% of stones and the rest of the 20% is composed of struvite, cystine, uric acid, and other stones.[27]

In supersaturation condition both homogenous and heterogeneous nucleation occurs. As a result, crystal growth precedes small crystal evolve into large crystals. Alternately, many small crystals aggregate to form crystal aggregates. Urine saturation can be increased by a

deficiency of crystal growth inhibitors i.e. citrate, magnesium, pyrophosphate, glycosaminoglycans by dehydration or over excretion of calcium in urine. Kidney stone formation is a complex process that occurs due to imbalance between promoters and inhibitors in the kidneys.[28]

1. Saturation

If increasing quantity of substances capable of crystallizing is added to pure water at a given temperature and pH eventually a high enough concentration is reached for crystal to form. When crystals begin to form, we state that the solution become saturated with the substances. When two or more substances combine to form the crystal e.g. calcium oxalate, the level of saturation is governed by the product of the concentration of two or more substances. The point at which saturation is reached and crystallization begins is referred to as the "solubility product". It is defined as the product of the molar concentration of the two substances at the point at which Saturation is reached.

Always the pH and temperature are specified for any crystallization process. Since urine varies widely in pH, this factor must be considered in any explanation of lithiasis. In urine, when the concentration of a substance reaches the point at which saturation would occur in water, crystallization does not occur as expected. Urine has the ability to hold more solute in solution than dose pure water. Although all elements and molecules in urine are suspended in water, the mixture of many electrically active ions in urine causes interactions that change the solubility of their elements. In addition, many organic chemical molecules such as urea, uric acid, citrate and mucoprotein of urine all mutually affect the solubility of other substances. For example, citrate is well-known to combine with calcium to form a soluble complex.[29]

2. Supersaturation

If a specified quantity of calcium and oxalate that would crystallize when placed in a solution of water at given pH and temperature is placed in urine, it will be held in solution. If the amount of calcium and oxalate is increased progressively in the equivalent quantity of urine at constant pH and temperature, the calcium and oxalate will stay in solution even though the solubility product has been exceeded. In doing this, we are actually creating supersaturation. This zone of supersaturation is called the metastable region.[30]

The quantity of substances in urine can be increased to a point at which urine will no longer hold it in solution. Then spontaneous nucleation of the crystals begins. The area of

supersaturation between the solubility product and spontaneous urinary crystallization is the metastable region for a given substances.

Electrical attraction or repulsion of ions in biologic solution is also involved in the stone forming crystallization process. Rollins and Finlayson (1973) studied electrical fields of urine. Solution and the effect of various additives on the electrical attraction of urinary substance. This type of biologic electrical activity is called Zeta Potential.[31]

3. Crystal Nucleation

Nucleation is the hard crystal formation in solution. It is a necessary in construction of kidney stone. Widespread CaP (Calcium Phosphate) and CaOx (Calcium Oxalate) crystalluria is a suggestion that urine of human is adequately super saturated with regard to those salts for their nucleation, sufficient growth & aggregation. Degradation of the cell following with epithelial damage of renal induces many layer vessels.[32]

The calculus matrix comprises lipids & vesicle membrane. Phospholipids of plasma membranes may be projected to support the nucleation of crystal. Lipids differentiated from renal calculi matrix raised the calcium oxalate crystals nucleation. Nucleation on plasma membrane may promote tubular retention of crystal (Lieske and Deganello *et al.*,1999).

There two types of nucleation:-

1) Homogenous Nucleation

In urine there is supersaturation with respect to calcium oxalate and these two ions form clusters. Most small clusters eventually disperse because the internal forces that hold them together are too weak to overcome the random tendency of ions to move away. Clusters of over 100 ions can remain stable because attractive forces balance surface losses. Once they are stable, nuclei can grow at level of supersaturation below that needed for their creation. The formation product marks the point at which stable nuclei become enough to create a permanent solid phase.

2) Heterogeneous Nucleation

If supersaturated urine is seeded with performed nuclei of a crystal that is similar in structure to CaOx, oxalate and calcium ions in solution will bind to the crystal's surface as they would on a seed crystal of calcium oxalate itself. The seeding of a supersaturated solution by foreign nuclei is called 'Heterogeneous nucleation'.

Cell debris, calcification on the renal papillae, as well as other urinary crystals, can serve as heterogeneous nuclei that permit calcium oxalate stone to form, even though urine calcium oxalate supersaturation never exceeds the metastable limit for homogeneous nucleation.[33]

4. Crystal Growth

Ions transfer out of a solution onto mounting crystal result into growth of crystal. (Wasserstein A, 2005) After nucleation, growth of crystal is the next main phase of formation of stone. Several molecules or atoms in over saturated liquid initiated making groups. When group is small, this is significant.

Growth of crystal is found by molecular shape & molecule size, the physical properties of material, defects, pH & supersaturation levels that may form in the structure of crystal.[34]

5. Crystal Aggregation

If numerous nuclei and crystals are formed spontaneously and float freely, these nuclei become active kinetically and bounce about in the urine. Under certain conditions, however, these nuclei can grow and may come close enough to each other to be bound together by various chemical forces. Therefore, nuclei or larger growing crystals may aggregate to form larger crystal masses. They may add additional crystals to their surfaces by the process of aggregation or they may grow by adding new crystal mass to their surfaces.[35]

6. Crystal Retention

Crystal material retention can be the result of connection between the cells & crystals & such a process is simulated to play an effective function in crystal retention.[36]

Symptoms

Kidney stones might produce no symptoms or may be associated one or several symptoms.[37] Some of the symptoms following-

1. **Flank pain:** it occurs due to blockage of the ureter, this leads to pain most commonly beginning in the flanks (the sides of a person's or animals body between the ribs and hips) or lower back and other radiation to the groin (area between the abdomen and the upper thigh on either sides if the body). This pain is often known as renal colic and typically comes in wave lasting 20-60 minutes.

2. **Pyuria:** when >10 pus cells/ micro liter present in the urine due to urinary tract infection or kidney stones.

3. **Haematuria:** the condition in which visible RBCs or 1ml RBCs/ liter is present in urine due to the inflammation in the filtration unit of the kidney this condition is called glomerolonephritis. Presence of RBCs can alter the colour of urine.

4. **Dysuria (painful urination):** it is a condition in which burning or discomfort happens during the urination process. It is more common in women than in men. In men, it is more common in older men than young men.
5. **Obstructive uropathy:** due to obstruction in urinary tract system there is a chance of urinary tract disease.

6. **Decrease urine flow:** When stone is blocked the ureter, than there is improper passage for urine which can cause decrease in flow of urine.

Classification

In the 19th century, the chemical characterization of urinary calculi was initiated by J.F. Heller and proposed (in 1860) a system for chemical investigation of kidney stone based on the hardness, colour and chemical reactions performed directly on the dry material. In fact, these studies on renal calculi can be considered the beginning of modern Clinical Chemistry.[38]

Kidney stone analysis implying wet chemistry qualitative reactions in order to identify the different cations and anions present in the calculus was the unique methodology used during the first four decades of the twentieth century. Unfortunately, the inadequacies of elemental chemical methods of calculi analysis were not recognized until the beginning of 1950, when it was demonstrated that the structure and internal arrangement of calculi, crucial in determining the mechanism of formation of the different kinds of stones, were impossible to identify using chemical methods and it was necessary to use compositional physical techniques, like X-ray diffraction. For clinical routine practice, in spite of its interest for scientific purposes. Consequently, it is necessary to establish a classification of renal calculi, in accordance to its composition and fine structure.[39]

On the basis of their composition, Kidney stones are broadly categorised into calcareous (calcium containing) stones and non-calcareous stones. Calcareous are radio-opaque. Stones are classified as shown in the table.[25]

A. Calcium

Randall In 1937 observed tiny calcium sub-epithelial plaques localized in the renal papillae. In the human autopsy studies, researchers found calcium deposits in the renal papillae (Randall plaques) of 1/3 patients who had the history of nephrolithiasis. Saeed R. Khan suggested that oxalate, calcium oxalate crystals of Randall plaque could provoke renal cell reactive oxygen species production, which could in turn mediate inflammation response, and induce expression of inflammation-related molecule, such as α-1-microglobulin, e-cadherin and osteopontin.

Lieske *et al.* (1996) described the adherence of CaOx crystals to African green monkey renal epithelial (BSC-1) cells and wild-type Madin-Darby canine kidney (MDCK) cells. Crystals like as calcium phosphate (CaP) and CaOx in the urine could induce the chemical injury in the renal epithelial cells, in turn may lead to cell death and subsequently cell regeneration. Then the crystals could adhere to the injured renal tubules.[40]

B. Calcium triple phosphate stones or Struvite

Struvite {(NH_4) $MgPO_4 \bullet 6H_2O$} is a bio mineral and are made up of magnesium ammonium phosphate, occurs more commonly in females, usually in existence of a urinary tract infection (UTI) with increase producing bacteria that affects the chemical balance of urine, renal tubular acidosis and hyper parathyroidism. It occurs at pH > 7.5. Struvite stone is called as infection calculi or urease calculi.[41]

Certain bacteria which can cause an increase in urine pH are related with these stones. The bacteria (often staphylococcus, klebsiella pseudomonas, and protease species) utilize urea in the urine to form ammonia and carbon dioxide. The ammonia is changed to ammonium which in turn, raises the urine pH and becomes available for the formation of magnesium ammonium phosphate crystals. Stone develop as jagged structure called "Stag horns" and can grow to be quite large.[42]

C. Uric acid stones

Urinary uric acid exists in an insoluble form at pH < 5.05 and forms crystals. About 7-10% of stone are made up of uric acid which is actually crystal that is end product of purine metabolism, a nitrogen compound found in the proteins. These stones form because the urine becomes supersaturated with uric acid or when the urine volume is low. Frequently urinary pH is very low and at these low pH (5.4 or below) undissociated uric acid is very insoluble

leads to formation of uric acid stone and also develop in patient with gout. It is not visible on X- rays and dissolved when the urine is alkalinized (with potassium citrate) and found more common in male, due to genetic factor.[43]

D. Cystine stones

Cystine ($SCH_2CHNH_2COOH)_2$) is an amino acid in protein that does not dissolve well and easily precipates to form stones. Cystine stone, account for about 1-3% of all renal calculi and are formed in patients with cystinuria, an autosomal recessive disorder. The stones are greenish yellow, flecked with shiny crystallites and are moderately opaque with a rounded appearance. They are difficult to treat & requires life-long therapy. People who are homozygous for cystinuria excrete > 600 mg/day of insoluble cystine. Drugs containing sulfur, penicillamine and captopril are used. These sulfur containing drugs will bind to the sulphur component of the cystine. These stones are very hard and usually cannot be removed with lithotripsy. Although they are not made of calcium, they can be seen on X-ray.[44]

E. Xanthine stone

An increased urinary excretion of Xanthine may cause the formation of Xanthine stones. In some cases, feeding of purines rich diet while simultaneously administration of allopurinol can result in the xanthine ($C_5H_4N_4O_2$) stones formation. The medical management of xanthine stone is limited because its solubility. is necessarially invariable within the range of physiologic pH. So, currently advice includes intake of fluid of at least 3 liters/day.[45]

F. Protease related stones

An increasing incidence of HIV positive patients has led to widespread use of the protease inhibitor indianvir sulphate. Though, it can be related with urolithiasis 4- 12% of patients.[46]

Table 1: Types of stone with constituents and circumstance

Sr No.	Stone Type	Colour	Constituents	Circumstance	Percentage
1	Calcium oxalate	Black/dark brown	Calcium, oxalate	Acidic urine	74%
2	Calcium phosphate	Dirty white	Calcium, phosphate	Alkaline urine	72%
3	Uric acid	Yellow/ reddish brown	Uric acid	Persistently acidic urine	7-10%
4	Cystine	Pink/yellow	cystine	Rare genetic disorder	1-3%
5	Struvite	Dirty white	Calcium, ammonia, phosphate	Kidney infection	8%
6	xanthine	Brick red	xanthinuria	Extreme rare	0.5%

STONE INHIBITORS AND PROMOTERS

In the urine, there are some organic or inorganic compounds which can prevent the process of stone formation and some compounds are responcible or promote stone formation.

Inhibitors of the stone formation prevent crystal growth and aggregation by coating the surface of growing calcium crystals or by complexing with calcium and oxalate.[47]

a. Citrate

Citric acid is a tricarboxylic acid that circulates in blood to form complex calcium, sodium and magnesium at physiological pH (7.4). In our body, citrate is derived from endogenous oxidative metabolism. It is freely filtered through the glomelurus, Approximately 75% of citrate is reabsorbed in the proximal convoluted tubule (PCT), due to acid base balance. Citrate has been widely studied for its calculi inhibiting action in urine and found to be effective against the calcium oxalate (CaOx) and phosphate (CaP) stones. It effect by making a complex with calcium thereby reduce concentration of CaOx. Citrate directly effects on the surface of crystal rather than to an modification of the availability of free calcium. It also increases the CaOx aggregation inhibitory activity of various urine macromolecules (eg,THP) and may reduce the appearance of urinary OPN (osteopontin), which is an essential constituent of the protein matrix of urinary stones.

b. Pyrophosphate

COM crystal growth inhibits 50% by pyrophosphate. Pyrophosphate reduce the calcium absorption in the intestine. Oral administration of orthophosphate has shown minute benefit in prevention of stone reappearance.

c. Magnesium

Magnesium is the fourth most abundant mineral in the body and largely found in the bones. It is absorbed in the small intestines and excreted through the kidney. Just 1% of total body magnesium circulates in blood. Oral administration of magnesium will decrease the oxalate absorption and urinary excretion by forming complexes.

d. Osteopontin (Uropontin)

Osteopontin (OPN) is a negatively-charged aspartic acid rich phosphorylated protein that inhibits growth of CaOx crystals in a supersaturated solution. It is involved in the regulation of both physiological and pathological mineralization. OPN is present in the human urine at

levels in excess of 100 nM and synthesised inside the kidney. It is involved in various biologic processes including inflammation, wound healing, leukocyte recruitment and cell survival. OPN may inhibit the nucleation, growth and aggregation of crystals. In addition, also inhibits the crystal adhesion to epithelial cells.[48]

e. Glycosaminnoglycans (GAGs): it is one of the macromolecules present in the stone matrix. GAGs found in stone matrix were identified as hyaluronic acid and heparan sulphate. They play an important role in crystallization and may be act as inhibitors of CaOx crystal growth and crystal aggregation.[49]

f. Tamm-Horsfall protein (THP)

Tamm-Horsfall protein also known as uromucoid and isolated from urine. It is synthesized completely in the ascending limb of the loop of Henle's. THP production ranges from 30 to 60 mg/24 h in humans and most abundant protein in the urine of normal mammals. A significant increase in urinary THP indicates high-protein diet. Self-aggregation of THP might promote both heterogenous nucleation or formation of a protein and crystalline mass. Much controversy exists about whether THP is an inhibitor or a promoter of crystal aggregation. Most author believes that it is effective inhibitor of crystal aggregation in solutions with high pH, low ionic strength.[50]

g. Inter-a-inhibitor (IaI)

IaI belongs to the Kunitz-type protein superfamily, a group of proteins possessing a ordinary structural element (kunin). IaI is a glycoprotein composed of one light chain, also known as bikunin and 2 heavy chains (HC1 and HC2). Bikunin freely circulates in plasma and excreted in urine where it further degrades to fragments HI14 and HI8. It exhibits anti-inflammatory and antimetastatic functions in humans and animals. It can contribute to the regulation of crystal adhesion and retention inside tubules during formation of kidney stone.[51]

Table 2: Stone Inhibitors And Promoters

Promoting factors	**Inhibiting factors**	
	organic	**inorganic**
Calcium	Citrate	High urine flow
Oxalate	Magnesium	glycosaminoglycans
Sodium	pyrophosphate	Osteopontin (Uropontin)
Urate		Tamm-Horsfall protein
cystine		Protease inhibitor: inter a inhibitor
Low urine flow		

Low urine pH		
Tamm- horsfall protein		

Promoters of the stone formation enhance crystal nucleation, growth and aggregation by boost growing of crystals or by complexes with calcium, oxalate and other minerals present in urine. On the kidney cell surfaces, aggregates of protein, cell debris & other crystals can provide functionally same place for nucleation. The nucleation places can reduce super saturation which is needed to start crystallization and promote CaOx crystallization.[52]

On the surfaces of kidney cell, protein aggregates, cell debris and other crystals can provide equivalent site for nucleation.

a. Calcium

Calcium stones are an important pathological form that affects a high percentage of the population during life. The information available on their etiology, diagnosis, clinical presentation and treatment (medical and non-medical) is very extensive. In most cases (around 75%), stones mostly have a composition of calcium and generally present in the form of calcium oxalate (CaOx), whereas other types of stone formation are less frequent. Increased frequency of calcium phosphate (CaP) stones has been observed and above all among females, with bone-derived diseases and metabolic.

Among CaOx crystals, calcium oxalate monohydrate crystalline form is oxalate dependent, whereas calcium oxalate dihydrate crystalline form is calcium dependent. Calcium deposits can be situated within urinary cavities, in papilla and also in medullar collecting ducts.[53]

Calcium stone formation is a complex process that involves the numerous metabolic, anatomical and physiopathological mechanisms. A key factor in calculus formation is occurrences of supersaturated states of crystallization with the capacity to precipitate in urine. The saturation state of a substance is expressed as the proportion between a given substance and its solubility variable. The supersaturated condition of the CaOx is unrelated to the urinary pH. Metabolic disorders are, beyond any doubt, key factors in the formation and persistence of calcium lithiasis.[54] As mentioned above, the basis for calcium stone formation is supersaturation of the urine with stone-forming calcium salts (Table no. 3).

Table 3: Causes of calcium stone formation.

Condition	Definition	Causes
Hypercalciuria	Urinary calcium excretion > 200 mg/d	**Absorptive hypercalciuria:** ↑GI calcium absorption renal. **hypercalciuria:** impaired renal Ca absorption **resorptive hypercalciuria:** Primary hyperparathyroidism.
Hyperoxaluria	Urinary oxalate excretion > 40mg/d	**Primary hyperoxaluria:** genetic Ox overproduction dietary **Hyperoxaluria:** excessive dietary intake **Enteric hyperoxaluria:** ↑GI oxalate absorption
Hypocitraturia	Urinary citrate excretion < 320 mg/d	**Distal renal tubular acidosis:** impaired renal tubular acid Excretion. **chronic diarrhea syndrome:** GI alkali loss **Thiazide-induced:** hypokalemia **Idiopathic hypocitraturia:** High animal protein & sodium diet, excessive physical exercise.
Hyperuricosuria	Urinary acid excretion > 600 mg/d	Dietary urine excess, uric acid overproduction or over excretion
Hypomagnesuria	Urinary magnesium excretion < 50mg/d	Limited intake of magnesium-rich foods

b. Oxalate

Oxalate is a final substance of glyoxylate & ascorbate biotransformation which is a usual constituent of renal calculi. Hyperoxaluria is marked risk factor in process of formation of calculi. Chief oxalate in urine finds to be induced by biosynthesis of endogenous substances from precursors of oxalate which might or might not be a source of diet. Glycolic acid is a quick forerunner of oxalate which forms in regular food, divides markedly to the developing from inside biosynthesis of oxalate and is able to elevating urinary oxalate removal.[55]

c. pH

At pH < 5.5 increases risk of uric acid precipitation cause uric acid stones and pH > 6.7 increases risk of calcium phosphate precipitation and pH > 7 -7.5 increases urinary tract infection. pH between 5.8-6.2 considered normal and safe in prevention for formation of stones in the kidney or urinary tract system.[54]

d. Uric Acid

Uric acid is induced by xanthine oxidase from hypoxanthine and xanthine, which in turn are formed from purine. Uric acid is highly toxic to tissues than either hypoxanthine or xanthine. Its Increased or decreased concentrations in blood and urine are not medical conditions, but are related with different medical conditions.[56] Approximately one third of volunteers with

CaOx calculi have raised removal of urinary uric acid. Two possible mechanisms ware suggested: excessive dietary protein intake & endogenous uric acid over formation.[57]

Testing for and Diagnosing Kidney Stones

Confirmation of the presence of stones is very important. The analytical markers in urine and serum that are responsible for the clinical diagnosis of the urologic disorders are calcium, albumin, creatinine, urate and oxalate.[58] Available pharmaceutical drugs used in preventing and curing renal calculi are not effective in all patients and may produce adverse effects on long term use.[59] So, mostly herbal treatment is preferred. Renal calculi presence is diagnosed by the symptoms explained by the patients and the stones are recognized in the body with the help like X-rays.[60] Diagnostic steps for kidney stone are involve the following:

1. Establish the absence or presence of renal stones as soon as possible so that pain treatment can start if necessary. (Use imaging techniques, physical examination.)
2. If a renal stone is present, establish whether the stone is obstructing the urinary tract. (Use imaging techniques.)
3. Estimate the substance forming the crystal so that proper treatment and preventive measures can be taken. (Blood and urine tests.)
4. Blood urea nitrogen (BUN) and creatinine to assess kidney functioning
5. Urinalysis to check for crystals, bacteria, blood and white cells

Estimate any metabolic abnormalities in people with recurrent calculi (tests for blood and urine chemistries).

1. Physical Examination

Although they will seldom cause identification of disease, there are hints which help in the evaluation of calculi. The specific location of tenderness often does not point out the exact location of the stone. In case of blockage with infection, signs and symptoms of sepsis may be present.[61]

Table 4: location of stones and their symptoms

Calculi location	General symptoms
Kidney	Hematuria, vague flank algesia
Proximal part of ureter	Above abdominal algesia, flank algesia
Middle part of ureter	Flank algesia, abdominal algesia (anterior)
Distal part of ureter	flank algesia, abdominal algesia (anterior), dysuria, urinary frequency, renal colic

2. *Imaging tests*

For the determination of the presence of kidney stones, various imaging techniques are helpful. Five radiography modalities can be used to evaluate patients having renal colic: plain abdominal radiography, ultrasound, IVP, helical CT scan & MRI.

A. X –ray

This technique can only detect stones which contain calcium. It will miss pure uric acid or indinavir stones. X-rays can be done quickly and cheaply and are a quick, inexpensive and useful technique for monitoring growth of a kidney stone.[62]

B. Ultrasound

This test can detect both calcium and non-calcium types of stones. It often is not a good test to find a stone that is suddenly passing from the kidney through the ureter on its way to the bladder.[63]

C. Computerized tomography (CT or CAT scan

This is one of the best methods to detect kidney stones, especially when someone comes to the emergency room with severe pain (colic) due to a passing stone. It is more sensitive than ultrasound or X-ray. It can detect both calcium and non-calcium stone, although it may sometimes miss crixivan/indinavir stones.[64]

D. Intravenous pyelogram (IVP)

This is one of the oldest techniques for detecting kidney stone and still sometimes used. A special dye is injected into a vein. Then X-rays are taken of mid to lower abdomen. If a stone is present, a filling defect will be seen on the X-ray images. It is very useful for detecting stones in the ureter, especially if not seen by CT scan. This sometimes happens when the ureter is dilated or obstructed, but no stone is seen.[65]

E. CT urography

CT urography is a combination of CT and IVP. An injection of intravenous dye is given which outlines the parts of the kidney, ureters and bladder where urine collects. The images are viewed with a CT scanner. Traditional CT images are also generated. This test is particularly helpful as a step in the evaluation for blood in the urine (hematuria). It can show causes other than just stones. It is particularly useful in the evaluation of a kidney (renal)

diverticulum (a pouch that develops inside the kidney). Kidney stones and infections can form inside this pouch. It can also be associated with pain.[66]

F. Magnetic Resonance Imaging (MRI)

MRI techniques is used for diagnosing urinary tract blockage but do not yet accurately appear small stones, or ones that do not produce a blockage. Because no radiation is implied with magnetic resonance imaging, however, it may prove as a good option for pregnant women.[67]

G. Uroendoscopy

Uroendoscopy is a valuable technique in evaluation of kidney stones that have persistent or recurrent clinical signs related with the lower urinary tract. Uroendoscopy permits visualization of the bladder and urethral mucosa, detection of small calculi not seen on abdominal ultrasonography, evaluation for remnants of urachal, & direct visualization of masses that may be present.[68]

REFERENCES

1. Shelke T, Bhaskar VH, Gunjegaokar SM, Antre RV, Jha U. A pharmacological appraisal of medicinal plants with antilithiatic activity. World Journal of Pharmacy and Pharmaceutical Sciences. 2014 May 7; 3(7): 447-56.
2. Srinivas S, Venkanna B, Madan Mohan E, Krishna MC. Urolithiasis: overview. Int J Pharm Res Biomed Anal. 2012; 1(1): 20-31.
3. Verkoelen CF. Crystal retention in renal stone disease: a crucial role for the glycosaminoglycan hyaluronan?. Journal of the American Society of Nephrology. 2006 Jun 1; 17(6): 1673-87.
4. Grases F, Costa-Bauza A, Prieto RM. Renal lithiasis and nutrition. Nutrition Journal. 2006 Sep 6; 5(1): 1.
5. Zeren S, Satar N, Bayazit Y, Bayazit AK, Payasli K, Özkeçeli R. Percutaneous nephrolithotomy in the management of pediatric renal calculi. Journal of endourology. 2002 Mar 1; 16(2): 75-8.
6. Liu Y, Li S, Zeng Z, Wang J, Xie L, Li T, He Y, Qin X, Zhao J. Kidney stones and cardiovascular risk: a meta-analysis of cohort studies. American Journal of Kidney Diseases. 2014 Sep 30; 64(3): 402-10.
7. Afsar B, Kiremit MC, Sag AA, Tarim K, Acar O, Esen T, Solak Y, Covic A, Kanbay M. The role of sodium intake in nephrolithiasis: epidemiology, pathogenesis and future directions. European Journal of Internal Medicine. 2016 Jul 19.

8. Coe FL, Evan A, Worcester E. Kidney stone disease. The Journal of clinical investigation. 2005 Oct 3; 115(10): 2598-608.
9. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. Archives of Internal Medicine. 2004 Apr 26; 164(8): 885-91.
10. Siener R, Ebert D, Nicolay C, Hesse A. Dietary risk factors for hyperoxaluria in calcium oxalate stone formers. Kidney international. 2003 Mar 1; 63(3): 1037-43.
11. Heilberg IP, Schor N. Renal stone disease: causes, evaluation and medical treatment. Arquivos Brasileiros de Endocrinologia & Metabologia. 2006 Aug; 50(4): 823-31.
12. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. Kidney international. 2008 Jan 1; 73(1): 19-33.
13. Pak CY, Ohata M, Lawrence EC, Snyder W. The hypercalciurias Causes, parathyroid functions and diagnostic criteria. Journal of Clinical Investigation. 1974 Aug; 54(2): 387.
14. Hesse A, Siener R, Heynck H, Jahnen A. The influence of dietary factors on the risk of urinary stone formation. Scanning microscopy. 1993 Sep; 7(3): 1119-27.
15. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005 Mar 15; 71(6): 1153-62.
16. Rodman JS, Mahler RJ. Kidney stones as a manifestation of hypercalcemic disorders: hyperparathyroidism and sarcoidosis. Urologic Clinics of North America. 2000 May 1; 27(2): 275-85.
17. Buckalew Jr VM. Nephrolithiasis in renal tubular acidosis. The Journal of urology. 1989 Mar; 141(3 Pt 2): 731-7.
18. Gillespie RS, Stapleton FB. Nephrolithiasis in children. Pediatr Rev. 2004 Apr 1; 25(4): 131-9.
19. Kaw M, Silverman WB, Kabinovitz M, Schade RK. Biliary tract calculi in primary sclerosing cholangitis. American Journal of Gastroenterology. 1995 Jan 1; 90(1).
20. Flocks RH. Calcium and phosphorus excretion in the urine: of patients with renal or ureteral calculi. Journal of the American Medical Association. 1939 Oct 14; 113(16): 1466-71.
21. Ginalski JM, Portmann L, Jaeger PH. Does medullary sponge kidney cause nephrolithiasis?. AJR. American journal of roentgenology. 1990 Aug; 155(2): 299-302.
22. Edwards NL. The role of hyperuricemia and gout in kidney and cardiovascular disease. Cleveland Clinic journal of medicine. 2008 Jul; 75: S13-6.

23. Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, Ettinger B. Endogenous hormones and the risk of hip and vertebral fractures among older women. New England Journal of Medicine. 1998 Sep 10; 339(11): 733-8.
24. Soucie JM, Coates RJ, McClellan W, Austin H, Thun M. Relation between geographic variability in kidney stones prevalence and risk factors for stones. American journal of epidemiology. 1996 Mar 1; 143(5): 487-95.
25. Parmar MS. Kidney stones. Bmj. 2004 Jun 10; 328(7453): 1420-4.
26. Robertson WG. Pathophysiology of stone formation. Urologia internationalis. 1986 Jul 1; 41(5): 329-33.
27. Hautmann R, Lehmann A, Komor S. Calcium and oxalate concentrations in human renal tissue: the key to the pathogenesis of stone formation?. The Journal of urology. 1980 Mar; 123(3): 317-9.
28. Kim SC, Coe FL, Tinmouth WW, Kuo RL, Paterson RF, Parks JH, Munch LC, Evan AP, Lingeman JE. Stone formation is proportional to papillary surface coverage by Randall's plaque. The Journal of urology. 2005 Jan 31; 173(1): 117-9.
29. Robertson WG, Peacock M, Nordin BE. Calcium oxalate crystalluria and urine saturation in recurrent renal stone-formers. Clinical science. 1971 May 1; 40(5): 365-74.
30. Maikranz P, Holley JL, Parks JH, Lindheimer MD, Nakagawa Y, Coe FL. Gestational hypercalciuria causes pathological urine calcium oxalate supersaturations. Kidney international. 1989 Jul 31; 36(1): 108-13.
31. Basavaraj DR, Biyani CS, Browning AJ, Cartledge JJ. The role of urinary kidney stone inhibitors and promoters in the pathogenesis of calcium containing renal stones. EAU-EBU update series. 2007 Jun 30; 5(3): 126-36.
32. Vella M, Karydi MA, Coraci GI, Oriti R, Melloni D. Pathophysiology and clinical aspects of urinary lithiasis. Urologia internationalis. 2007 Aug 30; 79(Suppl. 1): 26-31.
33. Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. Pediatric Nephrology. 2010 May 1; 25(5): 831-41.
34. Qiu SR, Wierzbicki A, Orme CA, Cody AM, Hoyer JR, Nancollas GH, Zepeda S, De Yoreo JJ. Molecular modulation of calcium oxalate crystallization by osteopontin and citrate. Proceedings of the National Academy of Sciences. 2004 Feb 17; 101(7): 1811-5.
35. Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. Pediatric Nephrology. 2010 May 1; 25(5): 831-41.

36. Alok S, Jain SK, Verma A, Kumar M, Sabharwal M. Pathophysiology of kidney, gallbladder and urinary stones treatment with herbal and allopathic medicine: A review. Asian Pacific Journal of Tropical Disease. 2013 Dec 31; 3(6): 496-504.
37. Parks JH, Coe FL. The financial effects of kidney stone prevention. Kidney international. 1996 Nov 30; 50(5): 1706-12.
38. SILVERIO F, Gallucci M, Alpi G. Staghorn calculi of the kidney: classification and therapy. British journal of urology. 1990 May 1; 65(5): 449-52.
39. Grases F, Costa-Bauzá A, Ramis M, Montesinos V, Conte A. Simple classification of renal calculi closely related to their micromorphology and etiology. Clinica Chimica Acta. 2002 Aug 31; 322(1): 29-36.
40. Li JY, Liu J, Jiang J, Pumill C, Elaiho C, Zhang Y, Li S, Zhou T. Calcium oxalate calculi-induced clusterin expression in kidney. Urolithiasis. 2015 Oct 1; 43(5): 411-8.
41. Griffith DP. Struvite stones. Kidney international. 1978 May 31; 13(5): 372-82.
42. Doyle JD, Parsons SA. Struvite formation, control and recovery. Water research. 2002 Sep 30; 36(16): 3925-40.
43. Asplin JR. Uric acid stones. InSeminars in nephrology, 1996 Sep; 16(5): 412-424.
44. Martin X, Salas M, Labeeuw M, Pozet N, Gelet A, Dubernard JM. Cystine stones: the impact of new treatment. British journal of urology. 1991 Sep 1; 68(3): 234-9.
45. Pais VM, Lowe G, Lallas CD, Preminger GM, Assimos DG. Xanthine urolithiasis. Urology. 2006 May 31; 67(5): 1084-e9.
46. Gentle DL, Stoller ML, Jarrett TW, Ward JF, Geib KS, Wood AF. Protease inhibitor-induced urolithiasis. Urology. 1997 Oct 31; 50(4): 508-11.
47. Basavaraj DR, Biyani CS, Browning AJ, Cartledge JJ. The role of urinary kidney stone inhibitors and promoters in the pathogenesis of calcium containing renal stones. EAU-EBU update series. 2007 Jun 30; 5(3): 126-36.
48. Conte A, Roca P, Genestar C, Grases F. Uric acid and its relationship with glycosaminoglycans in normal and stone-former subjects. Nephron. 1989 Jul 1; 52(2): 162-5.
49. Hess B. Tamm-Horsfall glycoprotein-inhibitor or promoter of calcium oxalate monohydrate crystallization processes?. Urological research. 1992 Jan 1; 20(1): 83-6.
50. Atmani F, Mizon J, Khan SR. Identification of Uronic-Acid-Rich Protein as Urinary Bikunin, the Light Chain of Inter-α-Inhibitor. European Journal of Biochemistry. 1996 Mar 1; 236(3): 984-90.

51. Fleisch H. Mechanisms of stone formation: role of promoters and inhibitors. Scandinavian journal of urology and nephrology. Supplementum. 1979 Dec; 53: 53-66.
52. Siener R, Glatz S, Nicolay C, Hesse A. The role of overweight and obesity in calcium oxalate stone formation. Obesity research. 2004 Jan 1; 12(1): 106-13.
53. Robertson WG, Peacock M, Heyburn PJ, Marshall DH, Clark PB. Risk factors in calcium stone disease of the urinary tract. British journal of urology. 1978 Dec 1; 50(7): 449-54.
54. Pak CY. Kidney stones. The lancet. 1998 Jun 13; 351(9118): 1797-801.
55. Noonan SC, Savage GP. Oxalate content of foods and its effect on humans. Asia Pacific Journal of Clinical Nutrition. 1999 Mar 1; 8: 64-74.
56. Pak CY, Sakhaee K, Peterson RD, Poindexter JR, Frawley WH. Biochemical profile of idiopathic uric acid nephrolithiasis. Kidney international. 2001 Aug 31; 60(2): 757-61.
57. Henneman PH, Wallach S, Dempsey EF. The metabolic defect responsible for uric acid stone formation. Journal of Clinical Investigation. 1962 Mar; 41(3): 537.
58. Pak CY, Kaplan R, Bone H, Townsend J, Waters O. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. New England Journal of Medicine. 1975 Mar 6; 292(10): 497-500.
59. Jeong IG, Kang T, Bang JK, Park J, Kim W, Hwang SS, Kim HK, Park HK. Association between metabolic syndrome and the presence of kidney stones in a screened population. American Journal of Kidney Diseases. 2011 Sep 30; 58(3): 383-8.
60. Çiftçioglu N, Björklund M, Kuorikoski K, Bergström K, Kajander EO. Nanobacteria: an infectious cause for kidney stone formation. Kidney international. 1999 Nov 1; 56(5): 1893-8.
61. Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatric nephrology. 2010 Mar 1; 25(3): 403-13.
62. Pollack SS, Carlson GL. A comparison of x-ray diffraction and infrared technics for identifying kidney stones. American journal of clinical pathology. 1969 Dec 1; 52(6): 656-60.
63. Shah A, Owen NR, Lu W, Cunitz BW, Kaczkowski PJ, Harper JD, Bailey MR, Crum LA. Novel ultrasound method to reposition kidney stones. Urological research. 2010 Dec 1; 38(6): 491-5.
64. Primak AN, Fletcher JG, Vrtiska TJ, Dzyubak OP, Lieske JC, Jackson ME, Williams JC, McCollough CH. Noninvasive differentiation of uric acid versus non–uric acid kidney stones using dual-energy CT. Academic radiology. 2007 Dec 31; 14(12): 1441-7.

65. Mutgi A, Williams JW, Nettleman M. Renal colic: utility of the plain abdominal roentgenogram. Archives of internal medicine. 1991 Aug 1; 151(8): 1589-92.
66. Primak AN, Fletcher JG, Vrtiska TJ, Dzyubak OP, Lieske JC, Jackson ME, Williams JC, McCollough CH. Noninvasive differentiation of uric acid versus non–uric acid kidney stones using dual-energy CT. Academic radiology. 2007 Dec 31; 14(12): 1441-7.
67. Spencer JA, Chahal R, Kelly A, Taylor K, Eardley I, Lloyd SN. Evaluation of Painful Hydronephrosis in Pregnancy:: Magnetic Resonance Urographic Patterns in Physiological Dilatation Versus Calculous Obstruction. The Journal of urology. 2004 Jan 31; 171(1): 256-60.
68. Khan F, Borin JF, Pearle MS, McDougall EM, Clayman RV. Endoscopically Guided Percutaneous Renal Access:" Seeing Is Believing". Journal of endourology. 2006 Jul 1; 20(7): 451-5.