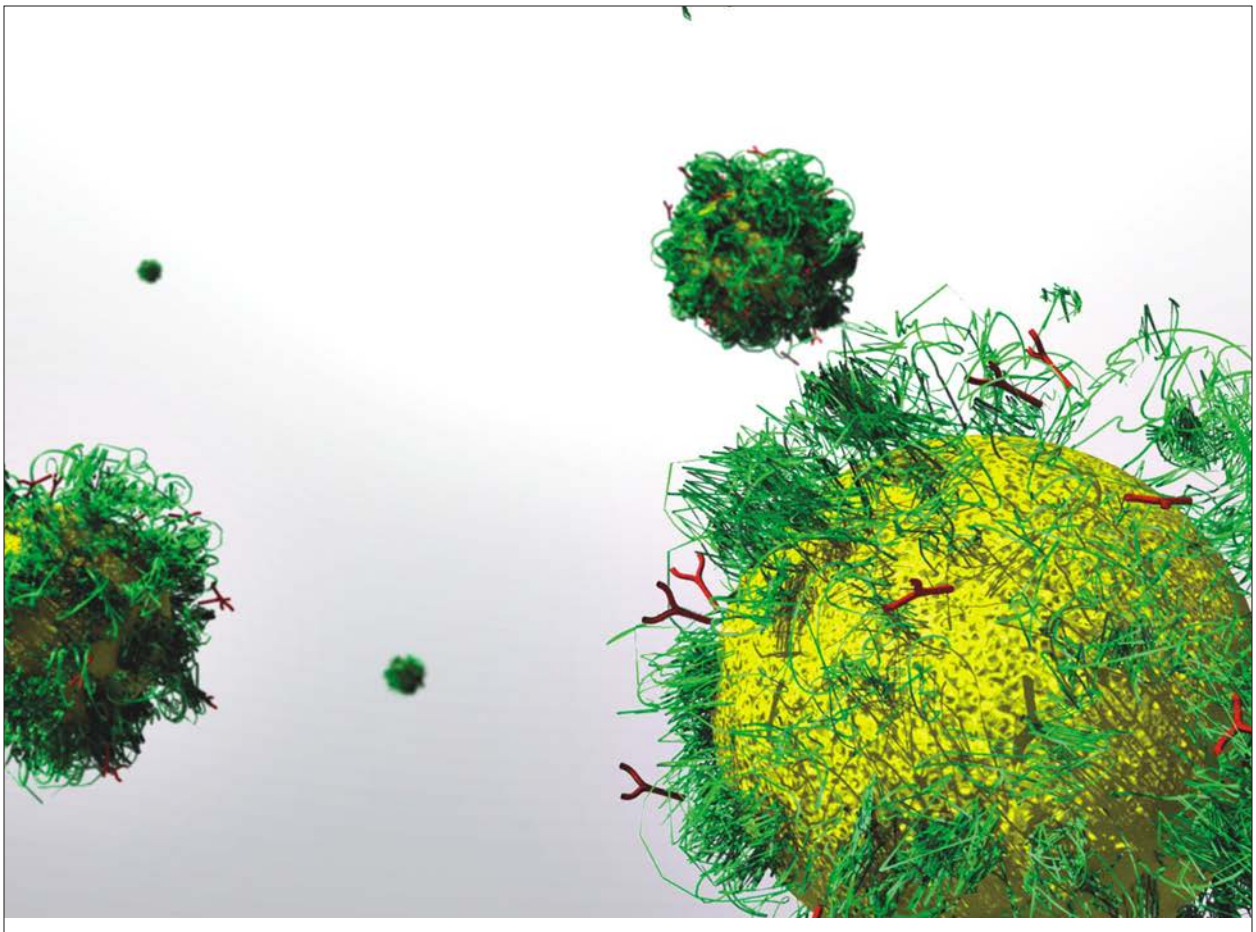

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Review Article
A Review on Epidemiology and Etiology of Renal Stone

Atul Sohgaura and Papiya Bigoniya

Radharaman College of Pharmacy, Ratibad, Bhopal, 462002 Madhya Pradesh, India

Abstract

Renal calculi are crystalline structures of calcium oxalate with associated risk factors like dehydration, high fat diet, animal protein, high salt intake and obesity. Crystals form in the distal tubule, nephron loop and/or collecting tubule have symptoms of severe pain and renal colic. Nephrolithiasis is a global problem affecting all geographical regions. This study compiles the epidemiology of renal calculi focusing on prevalence, occurrence and re-occurrence rate in global perspective. Literature of nephrolithiasis prevalence has been reviewed for Europe, Canada, American, East Asia, Gulf region, Japan, China and different parts of India. Etiology of nephrolithiasis was reviewed in detail for types, factors, symptoms, promoters and inhibitors. Renal calculi induction and progression mechanism was discussed with pathophysiology involved. Water and Food are directly related to occurrence of renal calculi, as a major concern correlation has been discussed. Depending on the type of renal stone, food which are to be avoided and preventive actions were discussed. Concise information was provided on the different experimental models of nephrolithiasis induction in animals. Understanding the pathophysiology of this disorder is necessary for the development of new therapeutic options and treatment. Nephrolithiasis is associated with chronic kidney dysfunction, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus etc. and understanding the pathophysiology is necessary to develop highly effective drugs.

Key words: Nephrolithiasis, renal calculi, epidemiology, etiology, symptom, risk factors, pathophysiology, chronic kidney dysfunction

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Corresponding Author: Papiya Bigoniya, Radharaman College of Pharmacy, Ratibad, Bhopal, 462002 Madhya Pradesh, India
Tel: +91 755 2896237 Fax: +91 755 2896664

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The formation of kidney stone is also known as renal calculi or crystal. It is a serious though not life threatening disorder prevalent throughout the world. In medical terminology condition of having urinary calculi is termed as nephrolithiasis and urolithiasis where the root word "Lith" meaning "a stone"[1]. Nephrolithiasis is common worldwide, often debilitating that has different etiology and pathophysiology. Copiousness of promoter and inadequacy of inhibitors mainly promote production and retention of crystals in renal tubules[2,3]. 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. Risk factors for supersaturation include dehydration, high fat diet, animal protein, high salt intake and obesity.

Typically, the crystals form in the distal tubule, nephron loop and/or in collecting system. Most crystals simply pass unnoticed into the urine. However, sometimes the crystals adhere to the epithelium of the tubules, particularly in the collecting system and form seed crystals that lead to the formation of stones. The stones may remain in the collecting system or may break off and lodge in the calyces, renal pelvis and ureter. Stones lodged within the urinary system cause occurrence of common symptom of nephrolithiasis, severe pain and renal colic that radiates from the lumbar region to the pubic region. Other symptoms include hematuria (blood in the urine), sweating, nausea and vomiting. Nephrolithiasis can be diagnosed in several ways, including computed tomography scans and an intravenous pyelogram. An IVP is a radiograph of the urinary system that uses a contrast medium such as iodine to reveal the structure of the renal pelvis, the major and minor calyces, the ureters and urinary bladder. The old Sanskrit literatures in India, the Vedas, the Puranas and the Samhita described first time about renal calculi and their remedies. The Chark Samhita had explained anatomy, physiology and pathology of renal calculi in Mutravahaashmari with diagnosis and its treatment. The Sushruta Samhita had also focused about surgery with descriptive explanation and type of renal calculi, characteristics of renal calculi, etiology and symptoms in Ashmari Nidana with scientific description and explained renal calculi treatment in Ashmari Chikitistia Sthanam[4,5].

Renal calculi is perceived as acute disorder but the growing stage of urolithiasis is a systemic disease that can lead to end stage renal disorder. The prevalence is increasing due to environmental cause and genetic predisposition[6]. On an average 6% woman and 12% men are affected with renal stone[7]. Recurrence rate of nephrolithiasis is 70-80% in males and 47-60% in females, with majority 80% of calcium oxalate stones[8,9].

URINARY SYSTEM

The urinary system is a group of organs that consists of two kidney and ureters with single bladder and urethra. This system mainly filters the blood stream excrete out the unwanted fluid and other substance through urine. Urine is liquid containing excess mineral or vitamins with waste product of metabolism. Urinary system along with other organ systems maintains homeostasis with acid base balance and water salt balance of blood.

Different function of urinary system:

- Excretion or elimination of metabolic waste product
- Regulation of fluid volume
- Regulation of different electrolytes
- Maintain the pH of blood
- Homeostasis maintenance
- Elimination of toxins
- Separation of urea and mineral salts
- Mineral and salt balance

RENAL CALCULI

A renal calculus is a solid crystalline mineral material that accumulate in the urinary system when one more crystal forming material separates from the supersaturated urine. Renal calculi results from the growth of crystal to form in to large lumps or aggregate of crystals or in to stone[10]. Primary component of renal calculi is salt, mineral and other constituents found in urine. Renal calculi grow slowly over several days to month. Renal calculi are found in different sizes, some are as small as like grain of sand or large as pearls and big as golf boll. Renal calculi sometime cover entire pelvis area of urinary system. They are smooth, spiky or asymmetric and jagged. Renal stone are mainly found in three colors as brown, yellow and reddish. Passing of renal calculi produces discomfort and the level of uneasiness depends upon the size of renal calculi. Tiny renal calculi may pass unnoticed with urine. Often renal calculi's grows to large size, that passing through urinary tract is noticed with some discomfort but if it is renal stone with rough or sharp edges it can be painful white passing through the urinary system. In some cases of

nephrolithiasis renal calculi cannot pass through the urinary system requiring medical intervention. If neglected it leads to substantial damage and produces several types of renal impairment[11].

Epidemiology of renal calculi: Kidney stone is one of the oldest recorded disorder of human and one of the major health burden. Now a days large number of peoples are affected with this disorder all over the world. Three common terms used in epidemiological study of renal calculi is incidence, prevalence and life time prevalence. The definition of incidence is the number of new renal stone patients found in a selective population at a particular time point. Prevalence is the total number of renal stone patients in a selective population at a particular time point and life time prevalence is the presence of old nephritic stone in number of patient. Nephrolithiasis is a common disorder responsible for significant human suffering as per studies and surveys done over the last half century reporting steadily increasing cases[7,12].

Nephrolithiasis is a global problem affecting all geographical regions throughout the globe. Annual approximate prevalence is 3-5% and approximate life time prevalence is 15-25%. Nephrolithiasis tend to be recurrent in most of the renal calculi patients. Recurrence rates of renal stone are approximately 10% $year^{-1}$, 50% over a period of 5-10 years and 75% over 20 years period[11]. The incidence rate of nephrolithiasis varies with geographical region of an individual country. The rate of recurrence of renal calculi in patients after 1st time occurrence is 14% at 1st year, 35% in 5th year and 52% in 10th year[13].

The comparative incidence of renal calculi in adults are higher in Western region as compared to Eastern region of the world. The risk rate of prevalence as reported throughout the globe is Saudi Arabia 20.1%, USA 13-15%, Canada 12% and Europe 5-9%[14,15]. This era of globalization is witnessing increase cases of acute renal injury and emerging epidemic of renal calculi among all age groups including children of East Asia mainly Macau, Taiwan, Hong Kong and China due to the use of different type of milk and milk product, like milk powder, melamine-tainted milk, cookies, candies and chocolates[16]. In the year 2008 approximate 2.9 lakhs cases were diagnosed with renal stones, including children below age of 3 year[17]. High incidence rate is reported in middle east (20-25%) due to hot climate with increased chances of dehydration[18]. In Japan, minimum 5.4% of the population have at least one time affected with renal calculi in their life time provided by the data of 1995-1987 nationwide survey on nephrolithiasis[6].

The countries with alarming occurrence rate of nephrolithiasis is British island, central Europe, North Australia, Scandinavian and Mediterranean countries. The stone forming belt of the world is identified as Egypt, Sudan, Saudi Arabia, Iran, UAE, Philippines, India, Pakistan, Thailand, Myanmar and Indonesia with cases of renal calculi in all age group including child below 1 year of age and adults over 70 years with a male to female ratio[19] of 2:1. Almost one million people in USA is affected with renal calculi and visit emergency department annually with an economic impact[20] of approximately 2.1-5.3 billion US$. In last decades, an increase of almost 50% was observed in diagnosis and treatment cost of nephrolithiasis[21]. North American children have 5 time increased prevalence of pediatric nephrolithiasis in last 10 years. Incidence of nephrolithiasis varies in different region of USA but is mostly found in South Eastern states as like North Carolina, Virginia, Georgia, Tennessee and Kentucky and has a combined name as stone belt of North America[22]. Approximately 7.5 lakh cases of renal calculi were found in Germany between 1979-2000 suggesting a continuously increasing trend in renal stone occurrence and approximately three-fold prevalence in population aged between 50-64 years[12,23]. Studies in UK identified and suggested that due to change of life style and diet, a gradually upward tendency in annual incidence and downward in the age of onset for nephrolithiasis has been observed[24]. Swedish renal stone studies based on epidemiology, showed recurrence rate of 70% after 10 years on the patients previously having minimum two renal calculi before the follow up period[25].

Approximate 2 million people in India is affected with nephrolithiasis every year and some parts of country has name denoted as a stone belt that is, Gujarat, Maharashtra, Punjab, Rajasthan, Delhi, Haryana and part of states on North East side[26]. Urinary stone are also found in south India due to high intake of tamarind in regular diet[27]. In upper urinary tract urolithiasis is found mainly in the form of pure calcium oxalate crystals as observed in case studies of AIIMS, New Delhi[28,29]. The Kutchchh and Saurashtra region of Gujarat also has higher prevalence of renal calculi. In India, approximate 50% of the population is affected with renal calculi, which may end up to renal damage or loss of kidney function[30]. The rate of nephrolithiasis incidence, mainly staghorn calculi is very high in Manipur and some reports indicates North Western region of India have also increased prevalence[31]. North Eastern part of Bihar in Purina division showed increase renal stone cases during 1999-2001[32]. In the last few decades occurrence of pediatric renal calculi cases were observed in some epidemiological studies[33].

ETIOLOGY OF RENAL CALCULI

Generally, nephrolithiasis is more common in male as compare to female, mainly six type of stones are found as calcium oxalate containing stone, calcium phosphate containing stone, cystine containing stone, uric acid stone, xanthine and struvite containing stone. Main causes of nephrolithiasis are hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, hypomagnesuria, gouty diathesis, etc.

Type of renal calculi:

- Calcium oxalates stone are crystalline component of calcium oxalate monohydrate, calcium oxalate dihydrate and calcium oxalate trihydrate
- Calcium phosphate stone have crystalline components like hydroxyapatite, calcium hydrogen phosphate, dihydrate, unusual form of calcium phosphate, tricalcium phosphate, ammonium magnesium, phosphate hexahydrate, ammonium magnesium, phosphate monohydrate, magnesium hydrogen, phosphate trihydrate, carbonate apatite and octacalcium phosphate. Calcium oxalate and calcium phosphate stones are prevalent with abnormality in urinary system like hypercalciuria, hypomagnesuria, hyperuricosuria, hyperoxolourea and hypocitraturia
- Uric acid stone are crystalline components of uric acid anhydrous and uric acid dehydrate, usually 5-10% of analyzed population with renal stone are affected with uric acid stone. Uric acid is a metabolic product and around 25% of patients with this stone also suffer from gout disorder. Main reason of this type of stone is low urine volume, hyperuricosuria and acidic urine pH
- Cystine stone are caused due to high level of essential amino acid, cystine in urine. Cystine stone usually occur in childhood and it is a rare inherited metabolic disorder affecting 1-3% analyzed population of renal stone
- Struvite stone are infectious urinary stone of ammonium magnesium phosphate hexahydrate or struvite. It is a fascinating inorganic phosphate mineral closely associated with chronic urinary tract infection due to some microorganism such as urease-producing bacteria. This bacterium split urea in to ammonium which is combined with magnesium and phosphate
- Medication caused renal stone are formation of renal calculi due to inappropriate large dose ingestion of drugs like ephedrine, ciprofloxacin, guaifenesin, indianvir, nelfinavir, oxypurinol, sulfa drug, topimarate and triamterene[34]

Urinary calculi promoters: Calcium, sodium, oxalate, uric acid, urate and cystine.

Urinary calculi inhibitors: Magnesium, potassium, pyrophosphate, citrate, glycosamino glycans kidney proteins such as nephrocalcin, osteopontin, tamm-horsfall protein, muco-protein, uropontin, crystal matrix protein, renal lithostathine, urinary prothrombin fragment 1, bikunin (inter-alpha inhibitor) and calgranulin. Citrate is the main complexer for calcium ions in the urinary track.

Nephrolithiasis induction: Nephrolithiasis get started with super saturation of urine caused by various reasons as age, sex, climate, diet, fluid intake, inheritance, etc. Super-saturation initiates abnormality in kidney morphology, change in urine flow, metabolic abnormality and urinary tract infection. The oxalate ion interacts with tubular cell of kidney and in this process mitochondria starts lipid signaling. Lipid signaling produces free radical provoking necrosis of renal cell, increase in stone formation and decrease in crystallization inhibitor induces nucleation process. Crystal are activated and a change in different physiochemical reactions produces aggregation and retention of crystal in renal tubule. Crystals are converted to osteoponin or concrete stone in chronic cases[3].

Factor affecting nephrolithiasis occurrence

Age and sex: Most vulnerable age for nephrolithiasis occurrence is 20-70 years. It is widely occurred in men as compared to women.

Diet: High content of protein, sodium and low level of calcium increases the risk of nephrolithiasis.

History of family: Family history of nephrolithiasis increased risk of the nephrolithiasis occurrence.

Dehydration: Nephrolithiasis predisposes with excretion of concentrated urine.

Hypertension: Hypertension increases the risk of the nephrolithiasis.

Obesity: Increase in Body Mass Index (BMI) also has increased risk of kidney stone.

Inflammatory bowel diseases and gastric bypass surgery: They affect the absorption of the calcium ion and increases the precipitation of calcium and other stone forming substance which causes nephrolithiasis[35].

Drug: Loop diuretics, antacids, acetazolamide, glucocorticoids, theophylline, vitamins D and C etc., has incidental correlation with occurrence of renal calculi.

Symptoms of renal calculi:

- Discomfort in the side and back and below the ribs. This discomfort usually occur 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

Nephrolithiasis that do not cause these expressions may show up on x-rays when the patients seek medical care for other complications, such as blood in the urine or reappearing urinary tract infections.

RENAL STONE FORMATION MECHANISM

Step 1-5: Initially homogeneous nucleation starts which progress to heterogeneous nucleation causing oxalates crystal formation following that membrane phospholipids redistribution occurs.

Step 6: Oxalate induces redistribution of phospholipid phosphatidy serine in renal cell surface. Macrophages remove and engulf damaged cells[36]. Which serves as a calcium oxalate crystal binding site triggering other membrane linked enzyme activity[37] (Fig. 1).

Step 7: The cytosolic phospholipase A_2 (cPLA2), is a highly attentive phospholipase enzyme that hydrolyze the acyl group in sn-2 position of phospholipids. Arachidonic acid and assorted lyso-phospholipids are some of the many by products of cytosolic phospholipaseA_2 which can trigger other signaling pathways in the cell[38]. Arachidonic acid and assorted lyso-phospholipids implicate renal epithelial cell injury[39]. Patients suffering with active renal calculi show elevated plasma and red blood cell membrane arachidonic acid[40].

Step 8-9: In the renal epithelial cell culture oxalate exposure directly causes activation of cytosolic phospholipase A_2 (cPLA2) and implicate oxalate action like change in mitochondrial function and gene expression through by product of cytosolic phospholipase A_2 (cPLA2) (arachidonic acid and lyso-phosphatidylcholine)[41,42].

Step 10-11: Generation of ceramide depends upon activation of cytosolic phospholipase A_2 and oxalate induced cytosolic phospholipaseA_2 activation[43]. The following different cellular responses are membrane damage, cellular injury, proliferation, cytotoxicity and renal cell damage produced by signaling molecule[44].

Step 12-15: 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[42].

DIET IN RELATION TO KIDNEY STONE

Presence of highly concentrated calcium, oxalate and phosphorus containing substances in urine can cause formation of kidney stones. Waste products of the food in the bloodstream are carried to the kidneys and excreted in urine. Diet and fluid intake are important factors out of several other factors that can promote or inhibit kidney stone formation. In susceptible persons, certain foods can promote stone formation but commonly not related to people who are not susceptible. The first step in prevention of kidney stones is to understand the causes and types of stone formed. Laboratory analysis of stones as it passes in urine or retrieved surgically or with a scope inserted through the urethra intothe bladder or ureter gives direct indication of type of stone. Blood and urine are to be tested for unusual levels of chemicals, such as calcium, oxalate and/or sodium to determine type of kidney stone. The information related to type of stone helps the health care provider to suggest diet changes that can prevent future kidney stone growth. Depending on the type of kidney stone, changes in consumption of sodium, animal protein, calcium, citrate, potassium and oxalate are to done. For example, limiting oxalate in the diet may help prevent

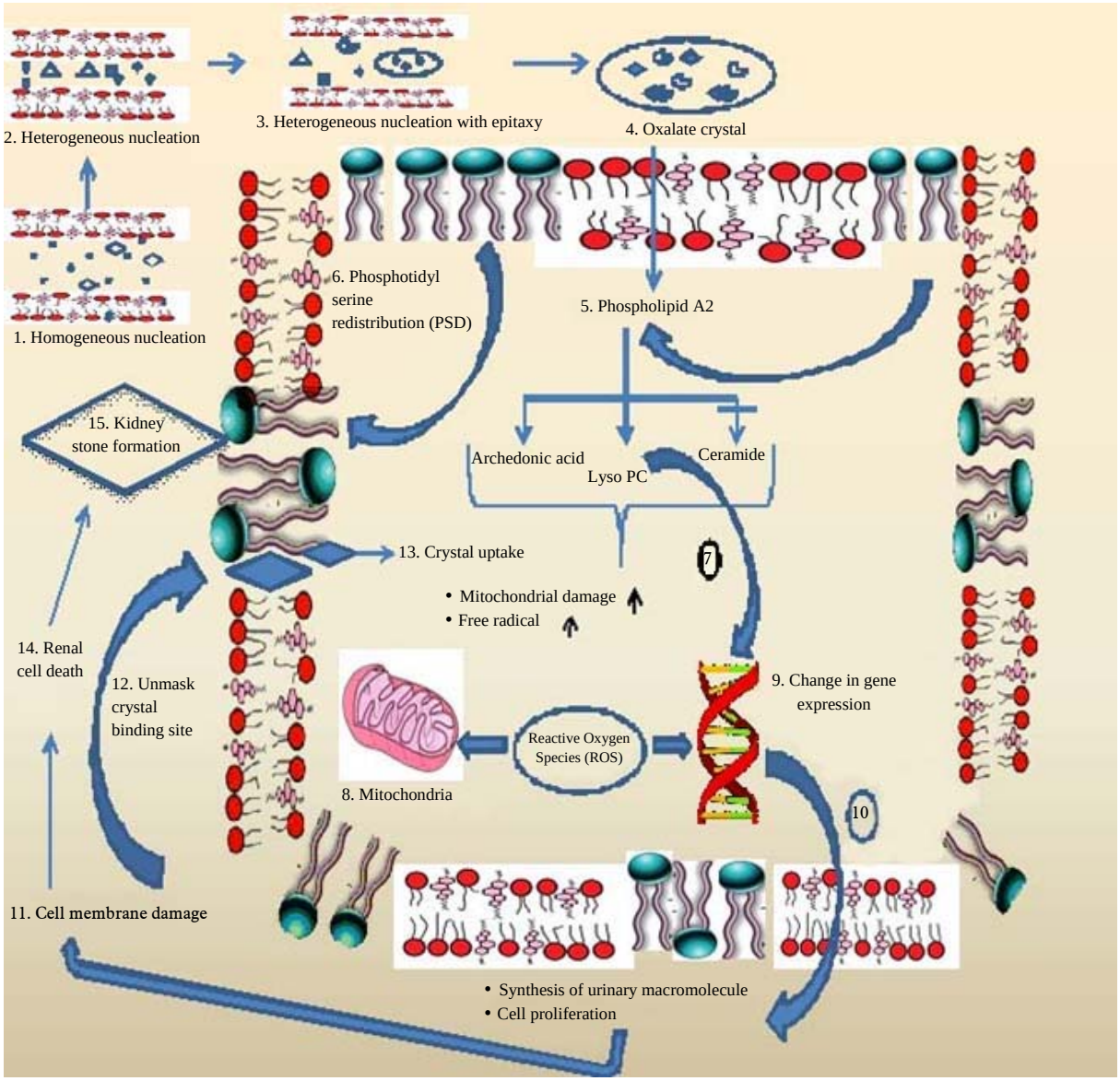

Fig. 1: Intracellular and extracellular events in calcium oxalate stone formation

calcium oxalate stones but may not be helpful in preventing uric acid stones. Following a special diet may be enough to prevent forming more kidney stones in early diagnosed cases and for chronic cases medications in addition to a special diet is needed.

High risk food: The risk of kidney stones increases with increased daily sodium consumption. High-sodium diet can trigger kidney stones as it increases the amount of calcium in urine as extra sodium causes to lose more calcium in urine. Low-sodium diet is recommended for the calcium oxalate or calcium phosphate stone prone. Instead of reducing calcium intake, focusing on limiting the sodium paired with calcium-rich and oxalate-rich foods will be beneficial. Current guidelines suggest limiting total daily sodium intake to 2,300 mg. Patients with calcium oxalate or calcium phosphate stones should limit their sodium intake to the U.S. RDA level, along with medications. Canned or commercially processed foods as well as restaurant-prepared and fast foods are sources of "Hidden" sodium. Getting too little dietary calcium can also cause oxalate levels to rise in blood. To prevent this, the amount of calcium should be appropriate to age group. More than 50 years older people should consume 1,000 mg calcium day^{-1}, along with 800-1,000 IU of vitamin D to help the body absorb the calcium.

Animal protein, such as red meat, poultry, eggs and seafood have high concentrations of purine. High purine intake leads to a higher production of uric acid that can

accumulate as crystals in the joints, or as stones in the kidneys. A high-protein diet also reduces levels of citrate, that helps prevent kidney stone forming. To prevent occurrence of common type of uric acid kidney stones, it is necessary to cut down high-purine foods and follow a healthy diet containing mostly vegetables, fruits, whole grains and low fat dairy products. Limiting sugar-sweetened foods and drinks containing high fructose corn syrup and alcohol is also helpful because these can increase uric acid levels in the blood. Eating less animal-based protein and eating more fruits and vegetables will help decrease urine acidity and this will help reduce the chance for stone formation.

Calcium oxalate kidney stones are the leading type of kidney stones. Oxalate is naturally found in many foods, including fruits and vegetables like beets, chocolate, spinach, rhubarb, tea and most nuts are rich in oxalate and colas are rich in phosphate, both of which can contribute to kidney stones. The persons prone to suffer from stones are advised to avoid these foods or to consume in smaller amounts. Some research suggests that limiting high oxalate foods may help reduce chance of forming further oxalate stone. Eating and drinking calcium and oxalate-rich foods together during a meal is a better approach than limiting oxalate entirely because oxalate and calcium are more likely to bind in the stomach and intestines before the kidneys begin processing thus making it less likely that kidney stones will form[45].

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. Health care providers recommend 2-3 L of fluid intake per day but people with cystine stones may need to drink even more. Water is best but other fluids such as citrus drinks also help prevent kidney stones. Some studies suggest citrus drinks like lemonade and orange juice protect against kidney stones because they contain citrate, which stops crystals from growing into stones. Citrate in the urine may prevent the calcium from binding with other constituents that lead to stones. In hotter weather, patients are required to drink more water to make up for fluid loss from sweating. For normal population, particular foods and drinks are unlikely to trigger kidney stones unless consumed in extremely high amounts. Some studies have shown that consumption of high quantity vitamin C in the form of supplements put at slightly higher risk of kidney stones as body converts vitamin C into oxalate. Caution should be exercised with consumption of vitamin C, vitamin D, fish liver oils or mineral supplements containing calcium since these supplements can increase the chances of stone formation in some people. The B6 may actually help people with high urine oxalate[46].

EXPERIMENTAL NEPHROLITHIASIS INDUCTION

Nephrolithiasis can be induced in rodents by induction of acute or chronic hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria or hypomagnesuria by using a variety of inducing agent like ethylene glycol with ammonium chloride, glycolic acid and sodium glyoxylate, ethylene glycol 0.75% v/v along with ammonium chloride 2% w/v oral^{-1} in drinking water is used as common nephrolithiasis inducing agent[47,48]. Diet containing 3% glycolic acid given for 28 days induces nephrolithiasis[49]. Glyoxylate induced calcium oxalate (CaOx) crystal in mouse kidney models is also reported by Liang *et al.*[50] and Peng *et al.*[51].

CONCLUSION

Nephrolithiasis remains life threatening disorder and cover almost all regions of the world. Exhaustive understanding of this disorder is necessary as lot of factors can induced this disease. Some drugs are associated with induction of nephrolithiasis. Understanding the pathophysiology of this disorder is also necessary for the development of new therapeutic options or treatment. This disorder is associated with chronic kidney dysfunction, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus and the metabolic syndrome. In India though nephrolithiasis is a commonly prevalence disease but pharmacotherapy is neglected emphasizing the need to develop highly effective drugs for treatment of nephrolithiasis.

SIGNIFICANCE STATEMENTS

Nephrolithiasis is a global problem affecting all geographical regions. Renal calculi are crystalline structures associated risk factors i.e., dehydration, high fat diet, animal protein, high salt intake and obesity.

Literature reviewed for nephrolithiasis prevalence in Europe, Canada, American, East Asia, Gulf region, Japan, China and different parts of India.

Renal calculi induction and progression mechanism was discussed with pathophysiology involved. Fluid intake and diet has been correlated with type of renal stone, as well as the precautions and preventive action were also discussed.

Relation of fluid intake and diet has been correlated with type of renal stone, precaution and preventive actions were discussed.

Concise information was provided on experimental models of nephrolithiasis induction in animals.

Nephrolithiasis is associated with chronic kidney dysfunction, bone loss, coronary artery disease, hypertension and type 2 diabetes mellitus signifying necessity of understanding the pathophysiology.

REFERENCES

1. Soni, A.B., 1999. A comparative study of Pratisaraneeya Kshara in the management of Arshas. Ph.D. Thesis, Gujarat Ayurveda University, Jamnagar, India.
2. Basavaraj, D.R., C.S. Biyani, A.J. Browning and J.J. Cartledge, 2007. The role of urinary kidney stone inhibitors and promoters in the pathogenesis of calcium containing renal stones. EAU-EBU Update Ser., 5: 126-136.
3. Hirose, M., K. Tozawa, A. Okada, S. Hamamoto and H. Shimizu *et al*., 2008. Glyoxylate induces renal tubular cell injury and microstructural changes in experimental mouse. Urol. Res., 36: 139-147.
4. Bhishagratna, K.K., 1911. Based on Original Sanskrit Text, Volume II. Kaviraj Kunja Lal Bhishagratna, Kolkata, pp: 25-30.
5. Tewari, M. and H.S. Shukla, 2005. Sushruta: The father of Indian surgery. Indian J. Surg., 67: 229-230.
6. Yoshida, O. and Y. Okada, 1990. Epidemiology of urolithiasis in japan: A chronological and geographical study. Urol. Int., 45: 104-111.
7. Stamatelou, K.K., M.E. Francis, C.A. Jones, L.M. Nyberg Junior and G.C. Curhan, 2003. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int., 63: 1817-1823.
8. Butterweck, V. and S.R. Khan, 2009. Herbal medicines in the management of urolithiasis: Alternative or complementary? Planta Med., 75: 1095-1103.
9. Al-Attar, A.M., 2010. Antilithiatic influence of spirulina on ethylene glycol-induced nephrolithiasis in male rats. Am. J. Biochem. Biotechnol., 6: 25-31.
10. Kok, D.J., 2002. Clinical implications of physicochemistry of stone formation. Endocrinol. Metab. Clin. North Am., 31: 855-867.
11. Moe, O.W., 2006. Kidney stones: Pathophysiology and medical management. Lancet, 367: 333-344.
12. Hesse, A., E. Brandle, D. Wilbert, K.U. Kohrmann and P. Alken, 2003. Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. Eur. Urol., 44: 709-713.
13. Sutherland, J.W., J.H. Parks and F.L. Coe, 1985. Recurrence after a single renal stone in a community practice. Miner. Electrolyte Metab., 11: 267-269.
14. Ramello, A., C. Vitale and M. Marangella, 2000. Epidemiology of nephrolithiasis. J. Nephrol., 13: 45-50.
15. Robertson, W.G. and H. Hughes, 1994. Epidemiology of Urinary Stone Disease in Saudi Arabia. In: Urolithiasis, Ryall, R., V. Bais, A. Marshall, L. Rofe and V.W. Smith (Eds.). Plenum Press, New York, ISBN: 978-1-4613-6091-9, pp: 453-455.
16. Bhalla, V., P.C. Grimm, G.M. Chertow and A.C. Pao, 2009. Melamine nephrotoxicity: An emerging epidemic in an era of globalization. Kidney Int., 75: 774-779.
17. Guan, N., Q. Fan, J. Ding, Y. Zhao and J. Lu *et al*., 2009. Melamine-contaminated powdered formula and urolithiasis in young children. N. Engl. J. Med., 360: 1067-1074.
18. Potts, J.M., 2004. Essential Urology: A Guide to Clinical Practice. 2nd Edn., Humana Press, Totowa, New Jersey, ISBN: 9781592597376, pp: 129.
19. Lopez, M. and B. Hoppe, 2010. History, epidemiology and regional diversities of urolithiasis. Pediatr. Nephrol., 25: 49-59.
20. Pearle, M.S., E.A. Calhoun and G.C. Curhan, 2005. Urologic diseases in America project: Urolithiasis. J. Urol., 173: 848-857.
21. Wein, A.J., L.R. Kavoussi, A.C. Novick, A.W. Partin and C.A. Peters, 2007. Campbell-Walsh Urology. 9th Edn., Saunders, Philadelphia, pp: 609-653.
22. Van Dervoort, K., J. Wiesen, R. Frank, S. Vento, V. Crosby, M. Chandra and H.J. Trachtman, 2007. Urolithiasis in pediatric patients: A single center study of incidence, clinical presentation and outcome. J. Urol., 177: 2300-2305.
23. Strohmaier, W.L., 2000. [Socioeconomic aspects of urinary calculi and metaphylaxis of urinary calculi]. Urologe A, 39: 166-170, (In German).
24. Robertson, W.G., 2001. The Changing Pattern of Urolithiasis in the UK and its Causes. In: Eurolithiasis, Kok, D.J., H.C. Romijn, P.C.M.S. Verhagen and C.F. Verkoelen (Eds.). Shaker Publishing, Maastricht, Netherlands, pp: 9-11.
25. Ahlstrand, C. and H.G. Tiselius, 1990. Recurrences during a 10-year follow-up after first renal stone episode. Urol. Res., 18: 397-399.
26. Urology and Andrology Centre, 2016. Kidney stones. Services. http://www.dilipraja.com/stone.htm.
27. Ansari, M.S., N.P. Gupta, A.K. Hemal, P.N. Dogra, A. Seth, M. Aron and T.P. Singh, 2005. Spectrum of stone composition: structural analysis of 1050 upper urinary tract calculi from northern India. Int. J. Urol., 12: 12-16.
28. Singh, L.B.K., S.N. Prasad and P.P. Singh, 1977. Urinary bladder stone disease and common types of urinary stones found in Manipur. Asian Med. J., 20: 589-589.
29. Hussain, F., F.R. Billimoria, S.D. Bapat and P.P. Singh, 1987. Prevalence and Etiology of Urinary Stone Disease in North-East Bombay. In: Multidimensional Approach to Urolithiasis, Singh, P.P. and A.K. Pendse (Eds.). Himanshu Publication, Udaipur, India, pp: 71.
30. Chandigarh Tribune, 2000. Leafy vegetables 'cause' stones. Tribune News Service. http://www.tribuneindia.com/2000/20001102/cth3.htm.

31. Haldiya, K.R., N.S. Bhandari, M.B. Singh, V.K. Beniwal and J. Lakshminarayana, 1999. Chemical composition of urinary calculi in desert region of Rajasthan, India. J. Hum. Ecol., 10: 69-72.
32. Rao, T.V.R.K., S. Bano and M. Das, 2006. Epidemiology of urolithiasis and chemical composition of urinary stones in Purnia Division of Bihar. Indian J. Commun. Med., 31: 76-77.
33. Sharma, A.P. and G. Filler, 2010. Epidemiology of pediatric urolithiasis. Indian J. Urol., 26: 516-522.
34. Lowry, P.S. and S.Y. Nakada, 2007. Urinary Stones of Unusual Etiology. In: Urinary Stone Disease-The Practical Guide to Medical and Surgical Management, Stoller, M.L. and M.V. Meng (Eds.). Humana Press, Totowa, New Jersey, ISBN: 978-1-58829-219-3, pp: 345-367.
35. Zhang, C.Y., W.H. Wu, J. Wang and M.B. Lan, 2012. Antioxidant properties of polysaccharide from the brown seaweed *Sargassum graminifolium* (Turn.) and its effects on calcium oxalate crystallization. Mar. Drugs, 10: 119-130.
36. Verkleij, A.J. and J.A. Post, 2000. Membrane phospholipid asymmetry and signal transduction. J. Membr. Biol., 178: 1-10.
37. Cao, L.C., J.A. Jonassen, T.W. Honeyman and C. Scheid, 2001. Oxalate-induced redistribution of phosphatidylserine in renal epithelial cells: Implications for kidney stone disease. Am. J. Nephrol., 21: 69-77.
38. Dennis, E.A., 1997. The growing phospholipase A2 superfamily of signal transduction enzymes. Trends Biochem. Sci., 22: 1-2.
39. Shankland, S.J., 2000. New insights into the pathogenesis of membranous nephropathy. Kidney Int., 57: 1204-1205.
40. Baggio, B., A. Budakovic, M.A. Nassuato, G. Vezzoli, E. Manzato, G. Luisetto and M. Zaninotto, 2000. Plasma phospholipid arachidonic acid content and calcium metabolism in idiopathic calcium nephrolithiasis. Kidney Int., 58: 1278-1284.
41. Scheid, C., T. Honeyman, Y. Kohjimoto, L.C. Cao and J. Jonassen, 2000. Oxalate-induced changes in renal epithelial cell function: Role in stone disease. Mol. Urol., 4: 371-382.
42. Jonassen, J.A., L.C. Cao, T.W. Honeyman and C.R. Scheid, 2003. Mechanisms mediating oxalate-induced alterations in renal cell functions. Crit. Rev. Eukaryot Gene Expr., 13: 55-72.
43. Miller, C., L. Kennington, R. Cooney, Y. Kohjimoto and L.C. Cao, 2000. Oxalate toxicity in renal epithelial cells: Characteristics of apoptosis and necrosis. Toxicol. Appled Pharmacol., 162: 32-141.
44. Kolesnick, R.N. and M. Kronke, 1998. Regulation of ceramide production and apoptosis. Annu. Rev. Physiol., 60: 643-665.
45. NIH., 2016. Eating, diet and nutrition for kidney stones. U.S. Department of Health and Human Services, National Institutes of Health, USA. https://www.niddk.nih.gov/health-information/health-topics/urologic-disease/diet-for-kidney-stone-prevention/Pages/facts.aspx
46. Pendick, D., 2013. 5 steps for preventing kidney stones. Harvard Health Publications, Harvard Medical School. http://www.health.harvard.edu/blog/5-steps-for-preventing-kidney-stones-201310046721
47. Khan, S.R., 2004. Role of renal epithelial cells in the initiation of calcium oxalate stones. Nephron Exp. Nephrol., 98: e55-e60.
48. Sailaja, B., K. Bharathi and K.V.S.R.G. Prasad, 2011. Protective effect of *Tridax procumbens* L. on calcium oxalate urolithiasis and oxidative stress. Pharmanest-Int. J. Adv. Pharm. Sci., 2: 9-14.
49. Jain, S. and A. Argal, 2013. Effect of a polyherbal formulation on glycolic acid-induced urolithiasis in rats. Bull. Pharm. Res., 3: 40-43.
50. Liang, L., L. Li, J. Tian, S.O. Lee and Q. Dang *et al*., 2014. Androgen receptor enhances kidney stone-CaOx crystal formation via modulation of oxalate biosynthesis and oxidative stress. Mol. Endocrinol., 28: 1291-1303.
51. Peng, Z., W. Chen, S. Gao, L. Su and N. Li *et al*., 2014. Therapeutic effect of Xue Niao An on glyoxylate-induced calcium oxalate crystal deposition based on urinary metabonomics approach. J. Clin. Biochem. Nutr., 55: 6184-190.