CASE REPORT

An insight on mechanism and management of kidney stones and its recurrence

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ABSTRACT

Kidney stones (calculi) comprise mineral concretions which can form in both renal calyces and pelvis and can be free floating or associated with the renal papillae. It is an emerging urological condition that affects around 12% of the world’s population. Globally, the prevalence and recurrence of kidney stone disease are increasing, and there are limited effective treatment options. I manifest a brief general overview and then concentrate on risk factors, pathophysiology, and medical treatment of kidney stones. The major component of most stones is calcium oxalate, and many of them develop on a foundation of calcium phosphate known as Randall’s plaques, which are located on the renal papillary surface. The mechanism of stone formation is a complicated process that involves multiple physicochemical phenomena such as supersaturation, nucleation, growth, aggregation, and retention of urinary stone ingredients inside tubular cells. Cellular damage is also thought to enhance particle retention on renal papillary surfaces. There is currently no effective treatment or prevention for kidney stone recurrence. Recurrence prevention required behavioral and nutritional interventions, as significantly as pharmaceutical therapies tailored to the kind of stone. There is a great demand for recurrence prevention, which necessitates a deeper knowledge of the processes involved in the development of stones to design more effective medications. Open surgical lithotomy has given way to minimally invasive endourological procedures for the treatment of symptomatic kidney stones, resulting in lower patient morbidity, increased stone-free rates, and enhanced quality of life. As a result, furthering our knowledge of the biology of kidney stone development is a research focus for treating urolithiasis with novel medications.

KEY WORDS: Kidney stones, Mechanism of kidney stones, Prevention, Recurrence, Treatment

INTRODUCTION

Mineral concretions known as kidney stones (calculi) can form in the renal calyces and pelvis and can be free floating or attached to the renal papillae [Figure 1]. They are produced when a mineral in the urine becomes oversaturated, and they have both crystalline and organic components.[1] The prevalence and recurrence of kidney stone disease are rising globally, and there are few effective treatment options. Around 12% of people worldwide experience urolithiasis at some point in their lifetime,[2] Around 10–12% of males and 5–6% of females worldwide are thought to be affected by kidney stones.[3] It affects people of all ages, sexes,[4] and races, but between the ages of 20 and 49, it affects males more often than females.[3] Nephrolithiasis or urolithiasis, the term for stones that form in the urinary tract, develops when the urine is excessively supersaturated with a certain mineral, which causes crystal development, aggregation, and retention within the kidneys.[6] The incidence of nephrolithiasis in women is rising, although the lifetime recurrence rate is higher in males.[6] Proteins combine with
both inorganic and organic crystals to form kidney stones. Numerous solutes in the urine can crystallize, followed by lithogenesis. Many different underlying conditions might lead to the development of urinary tract stones. It is essential for direct management that clinicians investigate the underlying causes of nephrolithiasis. According to recent studies, urolithiasis has become more common over the past few decades in both developed and developing nations. This expanding tendency is thought to be related to alterations in dietary habits and lack of physical activity in one’s lifestyle. It is believed that metabolic syndrome, diabetes, hypertension, and obesity all increase the risk of developing stones. A kidney stone in the urine bladder, ureter, or kidney, causes symptoms that differ according to where it is located in the kidney, urinary bladder, or ureter. Stone development does not initially result in any symptoms. Later, indications and symptoms of the stone disease include obstructive uropathy (urinary tract sickness), flank pain (back pain), renal colic (extreme cramping pain), restriction of urine output, UTI, hematuria (bloody urine), and hydronephrosis (dilation of the kidney). These complications could result in discomfort from the stone’s proliferation, vomiting, and nausea among other symptoms. Symptomatic recurrence of kidney stones can vary widely among patients, with some having only isolated episodes and others having frequent recurrences, chronic pain, and debilitating with numerous surgeries. According to estimates, patients who do not use metaphylaxis had a relapse risk of secondary stone formations of 10–23% per year, 50% in 5–10 years, and 75% in two decades. With an estimated 50% recurrence rate over 5 years, stone formation is a frequent condition. The occurrence of stones has been progressively increasing during the past 50 years, and additional increases are anticipated due to changing lifestyles, dietary preferences, and global warming. On the other hand, those who get stones are more likely to develop hypertension, CKD, and end-stage renal disease. About 12% of the population in India is predicted to develop urinary stones, and of those, 50% may experience kidney function loss. Kidney stones may be treated in a variety of ways, such as open surgery, percutaneous nephrolithotomy, super-mini percutaneous nephrolithotomy, ureteroscopy, extracorporeal shock wave lithotripsy, and conservative methods.

**STONES AND THE URINARY TRACT**

The glomerulus produces the urine filtrate, which then travels into the tubules where reabsorption or secretions change their amount and composition. The proximal tubules are where most solute reabsorption takes place, while the distal tubules and collecting ducts are where small modifications to compositions in urine are made. Urine that is 95% water, 2.5% urea, and 2.5% a mixture of salts, minerals, enzymes, and hormones is concentrated through the Henle loop. Along with chloride, salt, glucose, and water, the required nutrients including proteins, amino acids, phosphate, calcium, bicarbonate, and potassium are also reabsorbed and returned to the bloodstream in the proximal tubules. Salt and acid-base balances in the blood are regulated by the distal tubule.

**CLASSIFICATION OF KIDNEY STONES**

Kidney stones’ chemical makeup can be impacted by irregularities in urine’s chemical composition. There are variations in the size, form, and chemical composition of stones (mineralogy). Stones in the kidneys are often divided into five kinds based on changes in the composition of minerals and pathophysiology, as follows [Figure 2].

**Calcium stones: Calcium oxalate (CaOx) and calcium phosphate (CaP)**

About 80% of all urinary calculi are calcium stones, which predominate among urinary calculi. The fraction of calcium stones may be purely composed of CaOx (50%) and CaP (CaP, also known as apatite) (5%) or a combination of both (45%). Practically, all kidney stones
contain CaOx, which can be found as monohydrate CaOx (COM, also known as CaC2O4·H2O, Weddellite), CaOx dihydrate (CaC2O4·H2O, COD), or a mixture of the latter, accounting for more than 60% of kidney stones. There are a variety of factors that can cause the occurrence of CaOx stones, including metabolic disorders, absorptive, renal leak, and absorptive hypercalciuria, hyperuricosuria, and hyperoxaluria. CaOx stones are typically promoted by urinary pH levels along with 5.0–6.5, however, CaP stones develop when the pH level is higher than 7.5. In comparison to other kidney stone types, the occurrence of calcium stones is more likely.

Urate (uric acid stones)
This accounts for around 3–10% of all stone kinds. Purine-rich diets, especially those packed with animal proteins, such as fish and meat, cause low urine volume, low urinary pH (pH 5.05), and hyperuricosuria symptoms. Aggravates the development of urates. Gouty arthritis patients are at risk of developing kidney stones. Idiopathic causes account for the majority of cases as for nephrolithiasis caused by uric acid, and in contrast to women, men are more prone to urate formation.

Magnesium ammonium phosphate stones or struvite
Struvite stones, also known as infection stones and triple phosphate stones, are quite frequent, and relatively common, occurring in 10–15% of cases. The most prevalent bacteria producing urease in individuals are Proteus mirabilis with persistent UTI, less prevalent pathogens include Pseudomonas aeruginosa, Klebsiella pneumonia, and Enterobacter. Urease is required to break down urea into CO₂ and ammonia, which raises urine’s pH (usually >7) and causes it to become more alkaline. Phosphate has lower solubility at alkaline pHs than at acidic ones so; it accumulates on the insoluble ammonium molecules as precipitates, resulting in the production of huge staghorn stones. Escherichia coli is not connected to struvite stones and is not able to split urea.

Cystine stones
Among all stone types, these stones make up <2%. It is a hereditary disease of cystine and amino acid transport. It causes an increase in cystinuria in urine excretions and it is an autosomal recessive condition brought on by an rBAT gene deficiency on chromosome 2 resulting in reduced cystine tubular absorption in the kidneys or cystine leakage into the urine. It causes the development of cystine stones because it does not dissolve in urine. Cystinuria homozygotes excrete more than 600 millimoles of soluble cystine daily. The only clinical symptom of this cystine stone illness is the formation of urine cysisteine.

Drug-induced stones
This represents 1% of all stone types. These stones are brought on by medications including guaifenesin, triamterene, atazanavir, and sulfa medicines. For instance, those who use the HIV medicine indinavir sulfate, a protease inhibitor, run the risk of getting kidney stones. Such lithogenic medications or their byproducts may deposit to produce a nidus or on already existing renal calculi. However, by interfering with the metabolism of CaOx or purine, these medications may also cause calculi to develop.

RISK FACTORS
Renal stone formation is a complex and multidimensional process. The production of kidney stones (calculogenesis) is regulated by both intrinsic (such as age, gender, and inheritance) and extrinsic (such as climate, geography, diet, mineral content, and water consumption all factors to consider) factors. In industrialized nations during the last
few decades, the occurrence of renal stones in both men and women has sharply increased. The risk factors for the development of kidney stones include supersaturation of the lithogenic promoter’s calcium, oxalate, phosphate, and uric acid in the urine. However, a crucial concern is also a decreased urine concentration of stone-inhibiting substances including citrate, potassium, and magnesium. Diet has a significant impact on these stone modulators’ urine levels.[25] Table 1 presents an overview of the potential reasons for kidney stone development.[15]

**MECHANISM OF FORMATION OF KIDNEY STONES**

Low urine volume, hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria, and changes in urine pH are a few of the complex and diverse pathophysiological processes underlying the development of calcium kidney stones.[26] Physical, chemical, and supersaturation alterations in urine play a role in the biological process of renal stone development. A solution is referred to as being supersaturated when it includes more dissolved material than the solvent would typically be able to dissolve.[27] In urine, solutes precipitate due to supersaturation, which causes nucleation and the formation of crystal concretions. In other words, crystallization happens when two ions’ concentrations in a solution reach their saturation points.[13] A liquid’s transition into a solid phase is influenced by the pH and particular excess chemical concentrations. Low urine output and urinary saturation levels for substances such as calcium, phosphorus, uric acid, oxalate, and cystine that can cause stones are potential crystallization risk factors.[22,28] However, it must be emphasized that there is a degree of disparity between crystallization promoters and urine inhibitors which usually determines the likelihood of stone development. During the mineral phase of stone development, indistinguishable occurrences occur in all stones. The sequence of processes that lead to stone synthesis, however, varies depending on the type of stone and the chemistry of the urine. Examples include the crystallization of calcium-based stones (CaP or CaOx) in super-saturated urine with minimal potency. CaOx solubility is hampered by uric acid, which also encourages the development of CaOx stones. Inappropriate controls and inhibitory chemicals prevent crystallization and it becomes safe.[25] The process that leads to stone development in the kidneys includes crystal nucleation, proliferation, accumulation, and retention.[15] Nucleation of crystals

The initial stage of kidney stone formation begins with the generation of the nucleus (also known as a nidus) super-saturated urine retained within the kidneys.[10] Unbound atoms, molecules, or ions in a super-saturated liquid

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Risk factors</th>
<th>Specifications</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Lifestyle habits and nutritional/dietary factors</td>
<td>Too much intake of animal proteins and salts and deficiency of chelating substances such as foods high in citrate, fiber, and alkali.</td>
</tr>
<tr>
<td>2.</td>
<td>Metabolic complications</td>
<td>Hyperoxaluria, hypercalciuria, hyperuricosuria, hypocitraturia, and gout history (deficient uric acid metabolism)</td>
</tr>
<tr>
<td>3.</td>
<td>Disorders of hypercalcemia</td>
<td>Acute hyperparathyroidism and other calcium metabolic disorders</td>
</tr>
<tr>
<td>4.</td>
<td>Composition of Urine</td>
<td>Extreme excretion of urinary crystallization promoters and decreased excretion of inhibitors (urine lacking in inhibitory chemicals)</td>
</tr>
<tr>
<td>5.</td>
<td>Low urine output</td>
<td>Limited water consumption (dehydration and completely saturated urine)</td>
</tr>
<tr>
<td>6.</td>
<td>UTI that reoccur</td>
<td>Urine pH abnormalities and alkalinization through bacterial urease (Proteus mirabilis)</td>
</tr>
<tr>
<td>7.</td>
<td>Inherited disorders/genetic predisposition</td>
<td>Stones have quite a long history. (genetic vulnerability); genetic monogenic gene illnesses (autosomal faulty gene disorders); renal tubular acidosis</td>
</tr>
<tr>
<td>8.</td>
<td>Abnormalities in anatomy</td>
<td>Defects in the polycystic renal disease, ureteropelvic junction stenosis, medullary sponge kidney, pyloureteral duplication, and horseshoe kidney are all examples of kidney defects</td>
</tr>
<tr>
<td>9.</td>
<td>Hypertension</td>
<td>Blood pressure &gt;130/90 mmHg</td>
</tr>
<tr>
<td>10.</td>
<td>Obesity</td>
<td>BMI &gt;25.0</td>
</tr>
<tr>
<td>11.</td>
<td>Changes in climate</td>
<td>Global warming, profession, geographical circumstances, and seasonal variations (higher in summer than winter)</td>
</tr>
<tr>
<td>12.</td>
<td>Intestinal malabsorption</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>13.</td>
<td>Intestinal oxalate deficiency – degrading bacteria</td>
<td>Oxalobacter formigenes</td>
</tr>
<tr>
<td>14.</td>
<td>Lithogenic medicines</td>
<td>The protease inhibitor indinavir (crixivan), sulfonamides (sulfadiazine), uricosuric agents, which has a poor solubility and promotes the development of calculi and ceftriaxone (large dosage over a lengthy period of time)</td>
</tr>
</tbody>
</table>
Crystallization can take place at reduced chemical pressures than needed for the production of the original nucleus if a nucleus has been formed (or if it has been moored, as well). In the heterogeneous nucleation stick together, which produces nuclei, RBCs, urinary casts, pre-existing epithelial cells, and other crystals in the urine can function as nucleating centers. The organic matrix’s mucopolysaccharide acts as a binding component that encourages heterogeneous nucleation and crystal aggregation. Therefore, one of the best methods to control kidney stones is the treatment that concentrates on nucleation intervention.

Crystal growth

A little, hard mass of stone known as crystal growth is created when urine crystals stick together. Preformed crystals are gathered together to form stones, or secondary crystal nucleation occurs within the matrix coating. When a nidus is complete, the total amount of free energy is reduced by affixing fresh crystal elements toward its surface. Consequently, the cluster’s surface energy increases the cluster’s free energy overall. Since stones grow slowly, they clog the kidney tubules over a prolonged period. Osteopontin and Tamm-Horsfall protein are the major organic matrix components that encourage the synthesis of CaOx stones. In vitro research on crystals made from human urine revealed a close relationship between organic matrix and calcium-containing crystals (proteins and triglycerides). It is generally accepted that cellular membrane lipids have a role during crystal formation.

Crystal aggregation

Aggregation is the process through which a tiny crystal dissolved creates a hard mass that adheres to relatively large stones. All CaOx urolithiasis models agree agglomeration of crystals is likely responsible for crystal retention inside the kidneys. The aggregation of crystals is regarded to be among the most crucial stage in the formation of stones.

Crystal-cell interaction

Crystal cell or crystal retention contact occurs when growing crystals link to the epithelial cells that surround the renal tubule. Patients with hyperoxaluria had their renal tubular epithelial cells damaged when they were exposed to high oxalate levels and COM crystals. Crystals migrate to the basal layer from the basolateral membrane of the cells as a consequence of crystal-cell interactions. Crystals could then be incorporated into cells closely and linked to the kidneys’ basement membrane. Nephrolithiasis may have a crucial beginning event related to the contact of renal epithelia and COM crystals on their surfaces. The enhanced adhesion force among crystals and damaged renal tubule epithelial cells facilitates CaOx crystallization. The proportion of crystals associated with epithelia is considered to be destroyed within cells through lysosomes and/or macrophages before being excreted in urine.

Anionic proteins such as renal prothrombin fragment-1 are released by injured cells, and COM crystal clumping is brought on by these compounds. Among the variables hypothesized to play a role in kidney cell damage, one of them is reactive oxygen species. As a result, limiting renal oxidative stress may be a beneficial treatment technique.

A location of crystal adhesion is created when damaged cells enhance the inversion of their cellular membranes, which would be weakly acidic in the urine microenvironment. Crystals of COD are somewhat more likely than COM crystals to bind to its inverted membrane of anions. Even though the specific processes of crystal-cell interaction have not yet been completely identified, regulating crystal-cell retentions is among the greatest approaches to curing urolithiasis.

CaOx crystal endocytosis

Endocytosis is also characterized as the initial stage in the formation of kidney stones or crystals that were already received through the renal tubular cells. COM crystals quickly cling to microvilli on the surface of the cell before internalization, thus according to studies on how tissue culture crystals interact with cells. It is possible to prevent COM crystals from clinging to cell membranes by crystals being coated by citrate, glycoproteins, and glycosaminoglycans which are examples of such compounds, among other polyanion substances that comprise tubular fluid and urine. There are numerous intracellular and extracellular processes that are involved in the creation of stones. Stone formation might be prevented by modulators that target the processes from crystal retention to supersaturation. Similarly, blocking the expression of crystal-binding molecules on the membranes of the epithelial cell (such as monocyte chemoattractant protein-1, hyaluronic acid, sialic acid, and osteopontin), there may be a different way to prevent the formation of stones. The list below provides an overview of the numerous phases involved in the production of stones [Figure 3] or crystals being absorbed by renal tubular cells. Studies on how tissue culture crystals interact with cells have shown that COM crystals readily adhere to microvilli on the cell surface before internalizing. COM crystals begin to form tiny clusters that precipitate when the bulk free energy of the cluster is smaller than the liquids. The combination of charged, soluble molecules such as oxalate and calcium, for example, leads to the creation of insoluble CaOx crystals. Free-particle or fixed-particle mechanisms may be used to generate nucleation in the kidney. If promoters in excessively saturated solutions are greater than inhibitors, nucleation will begin.
may be prevented from adhering to cell membranes by crystals being coated by substances such as Citrate, glycoproteins, and glycosaminoglycans, among other polyanion substances present in tubular fluid and urine.[29] There are numerous cellular and extracellular processes involved in the creation of stones. Stone formation might be prevented by modulators that target the processes from crystal retention to supersaturation. Similarly, blocking the manifestation of crystal-binding molecules on the membranes of the epithelial cell (such as sialic acid, hyaluronic acid, monocyte chemoattractant protein-1, and osteopontin), there might be a different way to prevent the formation of stones.[29] The list below provides an overview of the numerous phases involved in the production process of stones [Figure 3].

**Apoptosis and cell injury**

CaOx (high oxalate) crystal exposure results in epithelial cellular damage, it serves as a risk factor for future stone development.[38] CaOx crystal deposits in the kidneys enhance the generation and expression of macromolecules that may induce inflammation.[39] Crystals may be transported to the interstitium as well as endocytosed through cells. According to some theories, damaged cells form a nidus that encourages particulate retention in the renal papillary region.[40] In individuals suffering from severe primary hypercalcemia, renal tubular cells are destroyed, and crystals bind to them.[34] Cytosolic enzymes as well as prostaglandin E2 were released in greater amounts when CaOx crystals were added to Madin-Darby canine kidney cell lines.[41]

Furthermore, research utilizing animal models discovered that excessive quantities of CaOx crystals or oxalate ions appeared to be toxic and impair renal tubular cells.[29] According to some hypotheses, oxalate makes free radicals highly accessible by impeding the enzymes needed to break them down. Reactive oxygen species, for example, may weaken and potentially impair the mitochondrial membrane’s transmembrane potential. These incidents are recognized as early process characteristics in apoptosis pathways.[42]

The manifestation of cellular proteins is controlled through the mitogen-activated protein kinase p38 activation (p38 MAPK) signaling pathway. Transcriptional factors are phosphorylated and activated as a result of the p38 MAPK gene’s activation, which is activated by a variety of extracellular inputs or stressors, including UV light and proinflammatory cytokines.[43] Oxalate treatment enhances a gene expression change that triggers apoptotic signaling cascades within renal cells.[42] According to a study, when HK-2 cells are exposed to more oxalate, the transcriptional activity of the IL-2R beta gene is increased. This raises the degree of the beta protein of IL-2R, which enables cellular changes such as inflammation to occur.

Although the precise mechanisms of oxalate-induced activation are unknown, it may act on membranes of cells to initiate p38 MAPK signaling.[44]

**Genetic roots of formation kidney stone**

Uncommon stone disease is brought on by environmental variables combined with relevant genetic factors.[45] The efficient function of epithelial cells of the kidney is required for the generation of crystallization promoters as well as inhibitors. Cellular dysfunction influences ions along with citrate, oxalate, and calcium which affect the super-saturation of urine output.[15] Table 2 lists certain genetic conditions that result in the development of stones.

**Randall’s plaques**

Even though it is uncertain whether it affects all forms of stones or not, Randall’s plaques are thought to be a
Cl/H antiporter

Bicarbonate exchanger/soluble adenylate cyclase

A change of gene mutation induces nephrocalcinosis, hypercalciuria, and stone formation. Calcium reabsorption is impaired, resulting in nephrocalcinosis and hypercalciuria. Nephrocalcinosis, phosphate deficiency, hypophosphatemia, hypercalciuria, and stone formation. Stones, hypercalciuria

Hyperphosphaturia, hypercalciuria, nephrocalcinosis, low molecular weight proteinuria, and stone formation are all caused by an inactivating mutation. Nephrocalcinosis, magnesium depletion, hypercalciuria, and stone formation

Hypercalciuria

Table 2: Genes linked with gene products, hypercalciuria, and kidney phenotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Gene expression</th>
<th>Kidney phenotypic expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASR</td>
<td>Calcium-detecting receptor protein</td>
<td>A change of gene mutation induces nephrocalcinosis, hypercalciuria, and stone formation.</td>
</tr>
<tr>
<td>VDR</td>
<td>Vit. D receptor protein</td>
<td>Calcium reabsorption is impaired, resulting in nephrocalcinosis and hypercalciuria.</td>
</tr>
<tr>
<td>NPT2a/e</td>
<td>Cotransporter of sodium phosphate</td>
<td>Nephrocalcinosis, phosphate deficiency, hypophosphatemia, hypercalciuria, and stone formation.</td>
</tr>
<tr>
<td>sAC</td>
<td>Bicarbonate exchanger/soluble adenylate cyclase</td>
<td>Stones, hypercalciuria</td>
</tr>
<tr>
<td>CLCNS</td>
<td>CL/H antiporter</td>
<td>Hyperphosphaturia, hypercalciuria, nephrocalcinosis, low molecular weight proteinuria, and stone formation are all caused by an inactivating mutation.</td>
</tr>
<tr>
<td>CLDN16</td>
<td>Tight junction protein</td>
<td>Nephrocalcinosis, magnesium depletion, hypercalciuria, and stone formation</td>
</tr>
<tr>
<td>KLOTHO</td>
<td>Calcium homeostasis regulator/aging suppressor protein</td>
<td>Hypercalciuria</td>
</tr>
</tbody>
</table>

harbinger of the development of urinary stones. At the locations among Randall plaque, it is common to find CaOx stones attached to renal papillae. It is situated in the loop of Henle’s membrane of the interstitial basement. There have been CaP and purine (apatite) crystal compositions in plaques but apatite predominates. Randall plaques, which have been made up of CaP crystals and organic matrix, form anywhere along basement membranes of the relatively small loops of Henle before trying to spread out across the interstitial space and eventually reaching the urothelium. There is evidence that the creative stone made of CaOx is secondary to the formation of interstitial apatite crystals. Supersaturated urine includes crystals that cling to the urothelium, perhaps facilitating the formation of stones in the future.

Plaque is revealed through urine that is too saturated because of renal cell damage. Products produced by the destruction (degradation) of renal epithelial cells facilitate heterogeneous nucleation as well as crystal adhesion among renal cells. The Randall plaque becomes calcified as a consequence of oxidative stress. At both the distal and collecting tubules, cells could exhibit compounds such as CD44, osteopontin, phosphatidylserine, and hyaluronan that act as crystal-binding sites. Renal epithelial cells seen within the Henle loop as long as in collecting ducts create membrane vesicles on the basal surface that also causes a plaque to form. As a result, the idea has been proposed that the deposition of apatite crystals serves as a nidus for the formation of CaOx crystals by attaching to additional matrix molecules. The elements that lead to plaque formation as often as the relevant matrix molecules, however, are still unknown.

A kidney stone may be loose or connected to the glomerular papillae. Based on the fixed particle route, the start of CaP accumulation in the interstitium provides a nucleus enabling CaOx production. As a site of attachment for stone growth, CaP has built up in the Bellini ducts, the innermost medullary collecting ducts, and the Henle loops’ basement membranes. CaOx forms a permanent interstitial plaque at the locations of idiopathic stone formation. Unlike cystinuria stones, stones from distal tubular acidosis cling to plugs extending from Bellini’s dilated ducts, they have no connection to the renal lumen (found freely). Crystals of cysteine that has developed in the renal tubules, uric acid, CaP, or both can obstruct the collecting ducts at the end. When mineralization approaches the renal papillary surface and causes plaques to break, CaP crystals are released further into pelvic urine. The CaP crystals are exposed which are then covered by urinary macromolecules, which promote the formation of CaOx on CaP.

Renal stones inhibitors and promoters

The onset of the rate of agglomeration, supersaturation, crystal growth, nucleation, and any additional processes required for stone production are all inhibited by certain chemicals. Chemicals in urine often inhibit the formation of crystals. Tiny pyrophosphates and other inorganic anions, citrate and other tiny organic anions, as long as multivalent metallic cations such as magnesium and macromolecules such as urinary prothrombin fragment-1, osteopontin, glycoproteins, glycosaminoglycans, and Tamm-Horsfall proteins, are examples of urine antagonists. Some individuals tend to produce stones as a result of the inhibitors’ inconsistent effectiveness. However, if the crystals that have developed are still small, they typically pass unnoticed; they pass through the urinary system and excrete urine from the body. Depending on how they interact with the crystal, inhibitors can have a direct or indirect effect on the process. Inhibitory substances prevent crystal nucleation, aggregation, growth, or cell adhesion when they adhere to a crystal’s surface. Conversely, promoters are molecules that, through a variety of methods, help stones develop. Lipids in cell membranes (cholesterol, glycolipids, and phospholipids) are among the promoters, along with...
reduced urine volume, oxalate, sodium, calcium, cystine, and cysteine. The triggering of the parathyroid hormone also increases calcitriol hormone levels. Recurrent stone-formers were found to excrete more oxalate from their urine than citrate. Oxalate has been shown in studies to trigger a variety of signaling pathways in renal epithelial cells, as often it enhances the reabsorption of water, sodium, and chloride in the proximal tubule. In general, it has been hypothesized that the cause of stone formation is a mismatch between urinary stone inhibitors and promoters.

**RECURRENT OF STONES**

When a kidney stone causes symptoms in a patient, the simultaneous existence of an asymptomatic kidney stone may be regarded as a “recurrence.” Such stones can be monitored and not surgically addressed as they have no symptoms. Monitoring could show signs of a “recurrence” in the future, such as growth or passing with or without symptoms. Such monitoring could be important for evaluating the efficacy of preventative measures. Due to a predicted higher risk for subsequent symptomatic stone episodes, the growth of an asymptomatic stone or fresh stone formation might be defined as “metabolically active” [Figure 4].

**MANAGEMENT**

**Surgical management**

Extracorporeal SWL, rigid or flexible retrograde ureteroscopic stone fragmentation and retrieval (30–40%), and PCNL (5–10%) are the three most often used treatment methods for renal stones. Extracorporeal SWL is used 40–50% of the time worldwide. Depending on the treating physician’s experience, the stone’s features (size, location, and composition), and the patient, each of these treatments has a distinct adverse-effect profile and predicted success rate (body habitus, medical co-morbidities, and anatomy). Patients can anticipate rapid recovery durations, little associated morbidity, and high stone elimination rates with appropriate counseling and procedure selection.

**Shockwave lithotripsy**

High-energy acoustic waves are delivered non-invasively during SWL to break up kidney stones. An acoustic lens is used to focus the shockwave on the stone once it has managed to pass through the patient and is generated by electrohydraulic, electromagnetic, or other energy sources. Energy is released as the shockwaves approach and travel throughout the calculus, disrupting interior structures and fragmenting the stone. SWL frequently employs fluoroscopic

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**Figure 4:** A theoretical framework for kidney stone recurrence biology and associated symptom or imaging identification
Ureteroscopic fragmentation and retrieval

Ureteroscopy involves the administration of various tools, such as guidewires, balloon dilators, laser fibers, and baskets, in addition to gaining access to the stone. It involves passing an endoscope retrogradely from the urethra proximally toward the damaged ureter and kidney. Although ureteroscopy is comparatively non-invasive, it needs spinal or general anesthesia to reduce pain and the visceral reaction to ureteral and renal dilatation. The holmium yttrium-aluminum-garnet (Ho: YAG) laser is still the primary method of lithotripsy in most centers in developed nations despite the availability of flexible electrohydraulic lithotripters because of its quick absorption in water and low tissue penetration. When there are numerous or radiolucent (stones that cannot be seen on plain film), hydronephrosis, high-density stones, or obesity, ureteroscopy is preferred over SWL (holmium lasers can fragment all stone types). Although it is uncommon, ureteroscopy for renal stones in patients with bleeding diathesis or during pregnancy would be thought to be the safest course of action.

Percutaneous nephrolithotomy

PCNL, which is typically used for stones larger than 2 cm, involves the direct passage of an endoscope percutaneously through muscle, skin, and perirenal fat into the kidney. Renal access is made possible with the help of endoscopic or radiographic imaging methods, along with fluoroscopic and/or ultrasonographic guiding. Approximately 70% of all renal access for PCNL occurs in the lower-pole calyx worldwide, and it has been demonstrated that placing a ureteral catheter for retrograde contrast injection before cystoscopic placement greatly improves targeting and acquiring admission to the kidney. PCNL is regarded as the gold standard of therapy for patients with a stone burden >2 cm or staghorn calculi, replicating the benefits of open surgery while reducing hospital stays by 75%. For the majority of stones, PCNL is thought to be more effective than ureteroscopic procedures or SWL, although it is also more invasive. The figure provides an algorithm for the most effective methods of treating kidney stones surgically [Figure 5].

Medical management

Medicinal expulsive therapy and the treatment of renal colic

In the absence of contraindications, the first line of treatment for kidney stone pain (renal colic) is the use of NSAIDs and opioids if other painkillers do not work. Acetaminophen (paracetamol) administered intravenously appears to be just as effective as morphine. Antispasmodic use does not appear to have a noticeable effect. Proper hydration is necessary, along intravenous fluids should only be administered in the event of prolonged

Figure 5: An algorithm for the most effective methods of treating kidney stones surgically
vomiting because doing so increases discomfort and risk of complications (such as urine extravasation and rupture of the renal pelvis) rather than aiding in the evacuation of stones.\(^6\) Calcium channel blockers and adrenergic receptor antagonists, especially tamsulosin, have been demonstrated to broaden the distal ureter and improve the possibility of spontaneous stone removal, making them good medical expulsive therapy.\(^1\) Two recently published well-designed, randomized, placebo-controlled trials, one of which found efficacy only for larger stones (>5 mm in size), and the other of which found no efficacy for stones of any size, have recently criticized the effectiveness of these agents in promoting the passage of small distal ureteral stones (5 mm in size).\(^{1,62}\)

**Oral and percutaneous dissolution therapy of stones**

Only uric acid stones are typically successful for the oral breakdown of pre-existing stones. The same guidelines recommended for their prevention can be used to dissolve at least a portion of two-thirds of these stones: Adjusting the pH of the urine to 7.0, raising the volume of the urine, and reducing uricosuria with febuxostat or allopurinol.\(^63\) The transformation of insoluble kidney stones into more water-soluble forms using percutaneous solutions, such as 10% hemiacidrin or Suby’s solution, was made popular in the 1960s but is now rarely utilized. The percutaneous dissolving of kidney stones is labor-intensive and far less effective than modern minimally invasive removal procedures, although being moderately helpful for infection, uric acid, cystine, and brushite stones.\(^{64}\)

**APPROACHES FOR PREVENTING KIDNEY STONES**

By examining the fundamental reason for stone development, kidney stones can be prevented effectively to avoid the initial episodes of kidney stone development or their subsequent episodes, strict food management and drug use are often necessary. Dietary changes are a cost-effective public health program that can have a significant impact on society by preventing the early stages of kidney stone disease. Hence, the most effective preventive method for urolithiasis is dietary management.\(^{65}\) Patients should be told to drink more water to keep their urine production at least 2 l/day, regardless of the underlying cause of the stone illness or the drugs being used to treat it.\(^{66}\) Drinking more water and other liquids is the most basic and crucial lifestyle change you can make to avoid developing the stone disease. The urinary saturation is decreased and the CaOx crystallization promoters are diluted when enough fluid is consumed. According to a person’s specific metabolic abnormalities, dietary recommendations should be modified. Low oxalate diets and higher dietary calcium intakes are advised for people with absorptive hyperoxaluria.\(^{67}\)

High sodium intake increases the chance of developing stones by lowering calcium reabsorption in the renal tubules and raising urine calcium levels.\(^{68}\) Another recommendation is to limit animal proteins because they possess higher acid load due to their high sulfur-containing amino acid composition. Therefore, a high protein diet lowers the pH and nitrate level of the urine through bone reabsorption, promoting urine calcium excretion. You may therefore need to consume less fish, poultry, and meat and steer clear of foods containing vitamin D if there is excessively acidic urine.\(^{15}\) Nonetheless, it is advised to consume more potassium-rich vegetables and fruits.

Previously, it was advised to avoid dairy products and other foods with high calcium content from consumption by those who develop calcium stones. But until, it has been proven, that a person uses calcium excessively, those who are prone to kidney stone development must not be recommended to limit their calcium consumption.\(^{69}\) Intestinal oxalate absorption is increased with decreased calcium intake, which may enhance the chance of stone formation. In the intestinal lumen, calcium binds dietary oxalate; calcium supplementation may lessen oxalate absorption. There is controversy over the benefits of calcium supplementation. Because ascorbic acid is transformed into oxalate *in vivo* when vitamin C is present, it has been linked to the development of stones. Consequently, it is advisable to take as little vitamin C supplement as possible.\(^{70}\)

By consuming a diet high in vegetables and fruits, taking citrate as a supplement or on a prescription, or ingesting alkaline mineral waters, urine can be alkalinized to avoid the formation of cystine, uric acid, and CaOx stones. Gout must be treated for those who develop uric acid stones, while salt and protein intake must be limited for those who develop cystine stones. To prevent unnecessary struvite and CaP stones, urine must be acidified. The most vital step in the treatment of struvite stones is to acidify the urine.\(^{70}\) Careful follow-up is necessary for patients to ensure that the infection has vanished. However, more study is needed because the available therapeutic options are ineffective at preventing urolithiasis.\(^{15}\)

**CONCLUSION**

Kidney stones are fairly common. They develop whenever a mineral in urine gets oversaturated, and they include both crystalline and organic components. Despite significant advances in the development of new therapies for the management of urinary stones, the global occurrence of urolithiasis is rising. It is considered that metabolic syndrome, diabetes, hypertension, and obesity all increase the risk of developing stones. However, renal cell damage, crystal retention, cell apoptosis, Randall’s plaque, and related stone inhibitors or promoters are all recognized to play essential roles in kidney stone development.
Stones have been linked to metabolic and environmental-nutritional factors such as hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, excessive urinary acidity, cystinuria, and low urine volume. A variety of drugs are now available to correct metabolic disturbances and prevent the formation of recurring stones. The treatment of symptomatic kidney stones has evolved from open surgical lithotomy to non-invasive endourological treatments, resulting in reduced patient morbidity, higher stone-free rates, and improved quality of life. Besides this, comprehending the fundamental pathophysiology, etiology, and genetic modulation of kidney stone generation should lead to the discovery of new medications and management techniques for urolithiasis in the not-too-distant future.

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