**Urolithiasis and Its Causes- Short Review**

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**Abstract**

The process of forming stones in the kidney, bladder, and/or urethra (urinary tract) is called as Urolithiasis. Stones form twice as often in men as women. The hallmark of stones that obstruct the ureter or renal pelvis is excruciating, intermittent pain that radiates from the flank to the groin or to the genital area and inner thigh. The stone type is named after its mineral composition. The most common stones are struvite (magnesium ammonium phosphate), calcium oxalate, urate, cystine and silica. The most common type of kidney stones worldwide contains calcium. Preventative measures depend on the type of stones.

**Keywords:** Urethra, Struvite, Calcium Oxalate, Urate, Silicate, Cystine

**Introduction**

The formation of stone in the urinary system, i.e. in the kidney, ureter, and urinary bladder or in the urethra is called urolithiasis. ‘Urolithiasis’ = ouron (urine) and lithos (stone). Urolithiasis is one of the major diseases of the urinary tract and is a major source of morbidity. Stone formation is one of the painful urologic disorders that occur in approximately 12% of the global population and its re-occurrence rate in males is 70-81% and 47-60% in female. It is assessed that at least 10% of the population in industrialized part of the world are suffering with the problem of urinary stone formation. The occurrence of the renal calculi is less in the southern part when compared with other parts. The rate of occurrence is three times higher in men than women, because of enhancing capacity of testosterone and inhibiting capacity of oestrogen in stone formation. It has been found that the formation of urinary calculi dates back not only to 4000 B.C in the tombs of Egyptian mummies also in graves of North American Indians from 1500 to 1000 B.C. Stone formation is also documented in the early Sanskrit documents during 3000 and 2000 B.C. The problem of stone formation is considered as a medical challenge due to its multifactorial etiology and high rate of reoccurrence. Stone formation is also caused due to imbalance between promoters and inhibitors. The rate of occurrence is three times higher in men than women, because of enhancing capacity of testosterone and inhibiting capacity of oestrogen in stone formation.

**Types of Urolithiasis**

The stone type is named after its mineral composition. The most common stones are
are struvite (magnesium ammonium phosphate), calcium oxalate, urate, cystine and silica.\(^7\)

<table>
<thead>
<tr>
<th>Name of stone</th>
<th>Approximate incidence</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate</td>
<td>70% of all stones</td>
<td>Calcium, oxalate</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>10% of all stones</td>
<td>Calcium, phosphate</td>
</tr>
<tr>
<td>Uric acid</td>
<td>5-10% of all stones</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Struvite</td>
<td>10% of all stones</td>
<td>Calcium, ammonia, phosphate</td>
</tr>
<tr>
<td>Cystine</td>
<td>Less than 1% of all stones</td>
<td>Cystine</td>
</tr>
<tr>
<td>Medication-induced stones</td>
<td>Less than 1% of all stones</td>
<td>Composition depends on medication or herbal product (examples include indinavir, ephedrine, guaifenesin, silica)</td>
</tr>
</tbody>
</table>

**Calcium oxalate stones**

The most common type of kidney stones worldwide contains calcium. For example, calcium-containing stones represent about 80% of all cases in the United States; these typically contain calcium oxalate either alone or in combination with calcium phosphate in the form of apatite or brushite.\(^8\)\(^9\) Factors that promote the precipitation of oxalate crystals in the urine, such as primary hyperoxaluria, are associated with the development of calcium oxalate stones.\(^10\) The formation of calcium phosphate stones is associated with conditions such as hyperparathyroidism\(^11\) and renal tubular acidosis.\(^12\)

Oxaluria is increased in patients with certain gastrointestinal disorders including inflammatory bowel disease such as Crohn disease or patients who have undergone resection of the small bowel or small bowel bypass procedures. Oxaluria is also increased in patients who consume increased amounts of oxalate (found in vegetables and nuts). Primary hyperoxaluria is a rare autosomal recessive condition which usually presents in childhood.\(^13\)

Calcium oxalate stones appear as ‘envelopes’ microscopically. They may also form ‘dumbbells’.\(^13\) Calcium oxalate crystals in the urine are the most common constituent of human kidney stones, and calcium oxalate crystal formation is also one of the toxic effects of ethylene glycol poisoning. Hydrated forms of the compound occur naturally as three mineral species: whewellite (monohydrate, known from some coal beds), weddellite (dihydrate) and a very rare trihydrate called caoxite. Most crystals look like a 6 sided prism and often look like a pointed picket from a wooden fence. More than 90% of the crystals in urine sediment will have this type of morphology. These other shapes are less common than the 6 sided prisms, however it is important to be able to quickly identify them in case of emergency.\(^14\)

**Struvite stones**

About 10–15% of urinary calculi are composed of struvite (ammonium magnesium phosphate, NH\(_4\)MgPO\(_4\)-6H\(_2\)O).\(^15\) Struvite stones (also known as “infection stones”, urease or triple-phosphate stones), form most often in the presence of infection by urea-splitting bacteria. Using the enzyme urease, these organisms metabolize urea into ammonia and carbon dioxide. This alkalinizes the urine, resulting in favorable conditions for the formation of struvite stones. Proteus mirabilis, Proteus vulgaris, and Morganella morgani are the most common organisms isolated; less common organisms include Ureaplasma urealyticum, and some species of Providencia, Klebsiella, Serratia, and Enterobacter. These infection stones are commonly observed in people who have factors that predispose them to urinary tract infections, such as those with spinal cord injury and other forms of neurogenic bladder, ileal conduit urinary diversion, vesicoureteral reflux, and obstructive uropathies. They are also commonly seen in people with underlying metabolic disorders, such as idiopathic hypercalciuria, hyperparathyroidism, and gout. Infection stones can grow rapidly, forming large calyceal staghorn (antler-shaped) calculi requiring invasive surgery such as percutaneous nephrolithotomy for definitive treatment.\(^16\)

Struvite stones (triple phosphate/magnesium ammonium phosphate) have a 'coffin lid' morphology by microscopy.\(^17\) Magnesium, ammonium and phosphorus are the building
blocks for the formation of struvite crystals in urine. In addition, urine pH and its influence on the concentration of trivalent ionic phosphate (PO4-3) play a key role in struvite crystallization. As urine pH increases, H3PO4, H2PO4- and HPO4-2 are rapidly deprotonated (i.e., removal of hydrogen ions) increasing the concentration of PO4-3, a principal component and driving force for struvite crystal formation.

Uric acid stones

About 5–10% of all stones are formed from uric acid. People with certain metabolic abnormalities; including obesity may produce uric acid stones. They also may form in association with conditions that cause hyperuricosuria (an excessive amount of uric acid in the urine) with or without hyperuricemia (an excessive amount of uric acid in the serum). They may also form in association with disorders of acid/base metabolism where the urine is excessively acidic (low pH), resulting in precipitation of uric acid crystals. A diagnosis of uric acid urolithiasis is supported by the presence of aradiolucent stone in the face of persistent urine acidity, in conjunction with the finding of uric acid crystals in fresh urine samples. As mentioned above (section on calcium oxalate stones), patients with inflammatory bowel disease (Crohn disease, ulcerative colitis) tend to have hyperoxaluria and form oxalate stones. These patients also have a tendency to form urate stones. Urate stones are especially common after colon resection. Uric acid stones appear as pleomorphic crystals, usually diamond-shaped. They may also look like squares or rods which are polarizable. Patients with hyperuricosuria can be treated with allopurinol which will reduce urate formation. Urine alkalization may also be helpful in this setting. Patients with hyperuricosuria can be treated with allopurinol which will reduce urate formation. Urine alkalization may also be helpful in this setting.

Cystine stones

Cystine kidney stones are due to cystinuria, an inherited (genetic) disorder of the transport of an amino acid (a building block of protein) called cystine that results in an excess of cystine in the urine (cystinuria) and the formation of cystine stones. Cystinuria is the most common defect in the transport of an amino acid. Although cystine is not the only overly excreted amino acid in cystinuria, it is the least soluble of all naturally occurring amino acids. Cystine tends to precipitate out of urine and form stones (calculi) in the urinary tract. Small stones are passed in the urine. However, big stones remain in the kidney (nephrolithiasis) impairing the outflow of urine while medium-size stones make their way from the kidney into the ureter and lodge there further blocking the flow of urine (urinary obstruction). Obstruction of the urinary tract puts pressure back up on the ureter and kidney. Causing the ureter to widen (dilate) and the kidney to be compressed. Obstruction also causes the urine to be stagnant (not moving), an open invitation to repeated urinary tract infection. The pressure on the kidneys and the urinary infections results in damage to the kidneys. The damage can progress to renal insufficiency and end-stage kidney disease, requiring renal dialysis or a transplant.

The stone are responsible for all the signs and symptoms of cystinuria, including:

- Hematuria -- blood in the urine
- Flank pain -- pain in the side, due to kidney pain
- Renal colic - intense, cramping pain due to stones in the urinary tract
- Obstructive uropathy -- urinary tract disease due to obstruction
- Urinary tract infections

Silicate stones or drug induced stones

Very rarely, stones can form as a result of taking certain medications or herbal products and the subsequent build-up of chemicals from those products in the urine. Some of these are Loop diuretics, Acetazolamide, Topiramate, Zonisamide, Laxatives (when abused), Ciprofloxacin, Sulfa medications, Triamterene, Indinavir, Ephedrine, Guaifenesin, and products containing silica.

Causes of urolithiasis

Dietary factors that increase the risk of stone formation include low fluid intake and high dietary intake of animal protein, sodium, refined sugars, fructose and high fructose corn syrup, oxalate, grapefruit juice, apple juice, and cola drinks. Stone formation commonly occur due to inadequate urinary drainage, foreign bodies in urinary tract, microbial infections, diet with excess oxalates and calcium, vitamin abnormalities like vitamin A deficiencies,
excess vitamin D, and metabolic diseases like hyperthyroidism, cystinuria, gout, intestinal dysfunction etc. Calcium oxalate is considered as main constituent in the renal calculi.

**Calcium**

Calcium is one component of the most common type of human kidney stones, calcium oxalate. Unlike supplemental calcium, high intakes of dietary calcium do not appear to cause kidney stones and may actually protect against their development. This is perhaps related to the role of calcium in binding ingested oxalate in the gastrointestinal tract. As the amount of calcium intake decreases, the amount of oxalate available for absorption into the bloodstream increases; this oxalate is then excreted in greater amounts into the urine by the kidneys. In the urine, oxalate is a very strong promoter of calcium oxalate precipitation, about 15 times stronger than calcium. Other electrolytes

Aside from calcium, other electrolytes appear to influence the formation of kidney stones. For example, by increasing urinary calcium excretion, high dietary sodium may increase the risk of stone formation. Fluoridation of drinking water may increase the risk of kidney stone formation by a similar mechanism, though further epidemiologic studies are warranted to determine whether fluoride in drinking water is associated with an increased incidence of kidney stones. On the other hand, high dietary intake of potassium appears to reduce the risk of stone formation because potassium promotes the urinary excretion of citrate, an inhibitor of urinary crystal formation. High dietary intake of magnesium also appears to reduce the risk of stone formation somewhat, because like citrate, magnesium is also an inhibitor of urinary crystal formation.

**Vitamins**

Despite a widely held belief in the medical community that ingestion of vitamin C supplements is associated with an increased incidence of kidney stones, the evidence for a causal relationship between vitamin C supplements and kidney stones is inconclusive. While excess dietary intake of vitamin C might increase the risk of calcium oxalate stone formation, in practice this is rarely encountered. The link between vitamin D intake and kidney stones is also tenuous. Excessive vitamin D supplementation may increase the risk of stone formation by increasing the intestinal absorption of calcium, but there is no evidence that correction of vitamin D deficiency increases the risk of stone formation.

**Other**

There are no conclusive data demonstrating a cause-and-effect relationship between alcohol consumption and kidney stones. However, some have theorized that certain behaviors associated with frequent and binge drinking can lead to systemic dehydration, which can in turn lead to the development of kidney stones. The American Urological Association has projected that increasing global temperatures will lead to an increased incidence of kidney stones in the United States by expanding the "kidney stone belt" of the southern United States.

**Supersaturation of urine**

When the urine becomes supersaturated (when the urine solvent contains more solutes than it can hold in solution) with one or more calculogenic (crystal-forming) substances, a seed crystal may form through the process of nucleation. Heterogeneous nucleation (where there is a solid surface present on which a crystal can grow) proceeds more rapidly than homogeneous nucleation (where a crystal must grow in liquid medium with no such surface), because it requires less energy. Adhering to cells on the surface of a renal papilla, a seed crystal can grow and aggregate into an organized mass. Depending on the chemical composition of the crystal, the stone-forming process may precede more rapidly when the urine pH is unusually high or low.

Supersaturation of the urine with respect to a calculogenic compound is pH-dependent. For example, at a pH of 7.0, the solubility of uric acid in urine is 158 mg/100 ml. reducing the pH to 5.0 decreases the solubility of uric acid to less than 8 mg/100 ml. The formation of uric acid stones requires a combination of hyperuricosuria (high urine uric acid levels) and low urine pH; hyperuricosuria alone is not associated with uric acid stone formation if the urine pH is alkaline. Supersaturation of the urine is a necessary, but not a sufficient, condition for the development of any urinary calculus. Supersaturation is likely the underlying cause of uric acid and cystine stones, but calcium-based stones (especially calcium oxalate stones) may have a more complex etiology.

**Inhibitors of stone formation**
Normal urine contains chelating agents such as citrate that inhibit the nucleation, growth and aggregation of calcium-containing crystals. Other endogenous inhibitors include calgranulin (an S-100 calcium binding protein), Tamm-Horsfall protein, glycosaminoglycans, uropontin (a form of osteopontin), nephrocalcin (an acidic glycoprotein), prothrombin F1 peptide, and bikunin (uronic acid-rich protein). The biochemical mechanisms of action of these substances have not yet been thoroughly elucidated. However, when these substances fall below their normal proportions, stones can form from an aggregation of crystals. Kidney stones often result from a combination of factors, rather than a single, well-defined cause. Stones are more common in people whose diet is very high in animal protein or who do not consume enough water or calcium. They can result from an underlying metabolic condition, such as distal renal tubular acidosis, Dent's disease, hyperparathyroidism, primary hyperoxalururia or medullary sponge kidney. In fact, studies show about 3% to 20% of people who form kidney stones have medullary sponge kidney. Kidney stones are also more common in people with Crohn's disease. People with recurrent kidney stones are often screened for these disorders. This is typically done with a 24-hour urine collection that is chemically analyzed for deficiencies and excesses that promote stone formation.

Conclusion

The present review conveys information about the urolithiasis types and causes of urolithiasis. Among the all minerals deposition of calacium oxalate is the main causative factor for urolithiasis. The rate of occurrence is three times higher in men than women. The occurrence of the urolithiasis is less in the southern part when compared with other parts. Urolithiasis is more common in people whose diet is very high in animal protein or who do not consume enough water or calcium.

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