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AN UPDATE ON CURRENT CONCEPTS REGARDING KIDNEY STONE DISEASE

[1]Dr. Aieman Saeed, [2]Dr. Sharjeel Khan Samejo, [3]Dr. Hamza Naseer Meo

[1]King Edward Medical University, Lahore, Pakistan., [2]Latin American Medical School, Cuba, [3]Faisalabad Medical University, Pakistan.

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Abstract:

Crystal concretions in the kidneys are kidney stones. This is a prevailing health issue that is affecting about 12% of the total world's population. This disease can lead to renal failure, thus it is life-threatening. Kidney stone has multifactorial etiology, as multiple reasons can contribute to their formation. The most common type of stone is calcium oxalate formed on the papillary surface of the renal at Randall's plaque. The crystal formation mechanism is complex that results from various physicochemical events modulated by an imbalance among multiple factors that inhibit or promote urinary crystallization. Apoptosis of protein kinase pathways and cellular injury also promotes these events. At present, no 100% satisfactory drug is available that can prevent the kidney stone recurrence. Thus, research is of great importance to manage urolithiasis with the help of new drugs and to better understand the pathophysiology of kidney stone development. Therefore, this research paper aims at the provision of up to date information regarding kidney stone etiology, its pathogenesis, and various prevention approaches.

Corresponding author:

Dr. Aieman Saeed,

King Edward Medical University, Lahore, Pakistan.

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INTRODUCTION:

Mankind has been afflicted by this urinary stone disease since as back as 4000 B.C. [1] This is the most common urinary tract disease and kidney stones are formed and lodged mainly in the kidneys.[2] Their prevention has remained a serious problem even in this era of medical advancements. [3] Kidney stones not only damage the kidneys and causes renal failure, but also are responsible for diabetes, hypertension, and cardiovascular diseases. Besides, metabolic syndrome is also linked with kidney stone formation. [4,5]

Symptoms of kidney stones are linked with their location, whether they are in the ureter, kidneys, or urinary bladder. At the beginning of stone formation, no signs and symptoms are observable. Later, symptoms involve renal colic (intense pain), hematuria (bloody urine), flank pain (pain in the backside), urinary tract infections, obstructive uropathy, blockage in urine flow, and dilation of the kidney (hydronephrosis). [6,7] These conditions can also cause nausea, vomiting, and associated stone related sufferings. Thus, any delay in treatment can cost the quality of life, mortality rate and nation's economy. [8]

The kidney stone recurrence rate is increasing globally. The options of drugs are limited. This disease has no link with age, sex, and race, it affects everyone equally. But, it can occur more frequently in men with the age of 29- 49 years, as compared to women. [11] The relapsing rate of second stage stone formation is 11 to 23%/ year, 50% in 5 to 10 years, and 75% in 20 years if patients are not subjected to metaphylaxis. Therefore, prophylactic management is imperative.

Recent studies have linked this prevailing disease with lifestyle changes like lack of physical activity, overconsumption of junk food, and global warming. [9,10]

The Urinary System and Stones:

The urinary filtrate, which is formed in the glomerulus, passes into the tubules where the process of reabsorption or secretion of its content is carried out. Adjustment of the urine composition is carried out in the distal and collecting tubules and reabsorption of glucose, water, sodium, and chloride along with essential nutrients is done in proximal tubules. In the loop of Henle, urine is concentrated composed of 2.5% urea, 2.5 % salts, minerals, hormones and enzymes, and 95% water. The acid-base balance of the blood is regulated by the distal tubules.

Types of Kidney Stones:

Kidney stones vary in nature and are formed due to abnormal variations in urine composition by chemical changes. The main five types of kidney stones are giving below:

1. Calcium Stones

Almost 80% of the renal stones are calcium stones. The proportion of calcium stones can contain pure calcium phosphate (apatite) 5%, calcium oxalate 50%, or a mixture of both 45%. [12] Calcium oxalate salt is a prominent component of the majority of kidney stones in the form of CaOx monohydrate, dehydrate, or in a combination of both 60%. The main constituent of calcium stones is calcium hydrogen phosphate (brushite) or hydroxyapatite. [13]

Many factors like a renal leak, absorptive, resorptive and metabolic diseases, hyperuricosuria, hypercystinuria, hypocitraturia, and hyperoxaluria. Usually, urinary 5.0 to 6.5 pH initiates CaOx stones, on the other hand, calcium phosphate stones occur at pH above 7.5. [14,15]

2. Struvite Stones

Struvite stones are also referred to as triple phosphate stones or infection stones with an occurrence rate of 10- 15%. Struvite stones are usually formed due to urinary tract infections responsible for producing urease. Pathogens like Enterobacter, Pseudomonas, Klebsiella pneumonia, and Proteus mirabilis are well known for causing this infection. Urease is imperative in splitting urea to ammonia, raising the pH of urine by making it alkaline. Phosphate is more soluble in acidic urine than alkaline urine. When the pH of the urine rises, phosphate precipitates on to insoluble ammonium products, thus forming staghorn stones. Escherichia coli cannot split urine components, so it is not linked with this urine stone formation.

3. Uric Acid Stones

Among all stone types, uric acid stones account for 3 to 10%. Diet rich in purines like those high with animal protein results in low urine volume, hyperuricosuria, and low urine pH. This situation exacerbates uric acid stone formation. Idiopathic is the most prevalent cause of uric acid nephrolithiasis. The chances of these stone formation are higher in patients with gouty arthritis.

4. Cystine Stones

Cystine stones only comprise 2% of all types. The genetic disorder responsible for disruption in cysteine and amino acid transport causes an excess of cystinuria excretion in urine. This genetic disorder is autosomal and occurs due to a defect in the rBAT gene on chromosome 2. This defect results in impaired cystine renal absorption or its leakage in urine. As it doesn't dissolve in the urine, so the stone forms. Homozygous people for cystinuria can excrete up to 600 millimoles of insoluble cystine/day.

5. Drug-Induced Stones

Drug-induced stones only account for 1% of all the types. Drugs like atazanavir, triamterene, sulfa, and guaifenesin induce these stones in the kidneys. For example, people who are taking protease inhibitor indinavir sulfate to treat HIF infection, are prone to kidney stones. These drugs or their metabolites can accumulate on renal calculi or form nidus, these drugs can also trigger calculi formation by interfering in metabolic activities.

Mechanism of Renal Stone Formation

Renal stone formation is a biological process that includes supersaturation of urine and physiochemical changes. In supersaturation, more amount of solute is absorbed in comparison to the normal absorption process. As a result of abnormal absorption, solute precipitates and convert themselves into crystals. This transformation of liquid into solid crystal phase is influenced by specific excess of the concentration of ions beyond their saturation points and change in pH.

However, it is crucial to note that this stone formation process depends upon the urinary inhibitors and promoters of crystallization. If promoters of crystallization are suppressed by inhibitors then the system remains healthy and safe.
The main and important steps involved in stone formation like nucleation, growth aggregation, and retention of crystals within the kidneys are as follows:

1. Crystal Nucleation

The formation of the nucleus is the first step of stone formation. In supersaturated urine, ions, free atoms, and molecules began to form microscopic clusters. These clusters precipitate when their bulk free energy is less than that of liquid, for example, charged soluble molecules of oxalate and calcium combine to form calcium oxalate crystals that are insoluble. Nucleation can be a result of free or fixed particle mechanism. If in supersaturation environment, promoters exceed inhibitors, then nucleation begins.

Existing urinary casts, epithelial cells, RBC's and other crystals can provide nucleus centers during heterogeneous nucleation. [16] Mucopolysaccharide, the organic matter, acts as a binding agent and aggravates nucleation and crystal aggregation process. Besides, apatite structures serve as crystallization centers for stone formation, which are formed by nanobacteria. Various types of bacteria are responsible for aggravating different natures of stone formation, thus for stone disease treatment, the process of nucleation intervention is the best approach.

2. Growth of Crystal

When microscopic clusters in urine stick together to form a small hard mass, then this process is referred to as crystal growth. Once a nidus is achieved, the free energy began to decline with each new crystal component addition to its surface. A longer time is required for the stone to obstruct the renal tubules as the stone formation process is slow. Tamm Horsfall protein and osteopontin are CaOx stone formation promoters. The study has shown that there is an intimate association between organic matrix and calcium-containing crystals. [17,18]

3. Crystal Aggregation

Aggregation is a process in which small hard masses of crystals in solution stick together into one large mass. Research in CaOx urolithiasis has shown that crystal retention in kidneys is due to crystal aggregation. This step is considered as the most critical one among all others.

4. Crystal- Cell Interaction

This phase began when crystals come in contact with the renal tubule lining of epithelial cells. Crystals move from the basolateral side of cells to the basement membrane, where they can anchor themselves. An increased retention force between injured renal epithelial tubule cells and crystals promotes CaOx crystallization. Many of these crystals are engulfed by macrophages inside cells and are discharged within the urine.

When renal tubules get injured, cellular degradation releases several membrane vesicles that act as promoters of calcium crystals. Substances like renal prothrombin fragment 1 or other anionic proteins are produced by injured cells that trigger COM crystal assembling. Cells gain injury due to various factors and reactive oxygen species interaction is one of them.

The presence of the binding molecules like hyaluronan on Madin Darby canine kidney cells, or at proximal tubular epithelial cells defines the nature and place of deposition of COM crystals. Thus, by controlling crystal- cell interaction, urolithiasis can be treated.

- **Randall's Plaques**

Randall's plaques are considered as the antecedent origin of stone development. However, if it involves all the stone types or not and which pathogens are associated, it is unknown. At the sites of Randall's plaques, the majority of CaOx stones are found attached to renal papillae. Apatite is a dominant type, whereas purine crystals and calcium phosphate are also identified in plaques. Initially, at the basement of the loop of Henle a mixture of organic components and calcium phosphate crystals deposits, then they extend themselves into the interstitial space to the urothelium. This extension constitutes Randall's plaques.

Plaque is exposed by cell injury to supersaturated urine, and the cell degradation products enhance the heterogeneous nucleation, which further promotes stone attachment in renal cells. Oxidative stress triggers Randall's plaques. Binding sites for stones like CD44, osteopontin, phosphatidylserine, and hyaluronan, are exposed by cells at distal and collecting tubules. Moreover, membrane vesicles are produced by epithelial cells of the loop of Henle which leads to plaque development. Thus, the apatite crystal might act as a nidus for CaOx stone formation.

Kidney stones either float freely or attach to the renal papillae. According to the fixed particle pathway, inner medullary collecting ducts of the loop of Henle and Bellini act as attachment sites for stone formation. At the fixed sites of interstitial plaque, idiopathic stoner promoters develop CaOx. Plugs protruding from dilated Bellini ducts catch the stones of distal tubular acidosis. At the terminal collecting ducts, uric acid, cystine crystals, and CaP are formed in renal tubules. CaP crystals are exposed to urine upon the rupture of the renal papillary surface. Upon exposure, urine macromolecules settle upon CaP crystals and promote CaOx deposition there.

Urolithiasis Prevention:

Effective kidney stone prevention entirely depends upon the cause and type of stone formation. Basically, despite first or second stage treatment, proper diet management and medicine is the main thing. The nutritional management plan falls under the primary stone prevention approach and has been observed with positive results.

Patients are instructed to increase water intake to get an output of 2 liters/ day urine regardless of their drug treatment. Enough fluid intake promotes urine dilution and reduces urinary saturation which ultimately prevents CaOx crystallization. Dietary modification is imperative in patients with metabolic abnormalities, for instance, low oxalate and increase calcium diet is recommended for absorptive hyperoxaluria.

Less sodium and animal protein intake is recommended, as the former increases urinary calcium, and the latter increases acid load owing to its high sulfur-containing amino acids. Thus, patients with acidic urine, patients are advised to consume less fish, meat, poultry, and vitamin D, and increase the consumption of fruits and vegetables.

Patients with calcium stone issues are advised to reduce the intake of products with the high calcium content. But, reduced calcium intake can lead to an increase in oxalate absorption, which can also pose a risk to stone formation. So, calcium supplements are given which absorbs dietary oxalate in the gut. Vitamin C is also found associated with oxalate stone formation, thus it's supplement intake is also advised to reduce.

Diet high in fruits and vegetables, prescribed citrate, and alkaline mineral waters alkalinize the urine and prevent stone or uric acid, cystine, and calcium oxalate nature. Gout needs to be controlled for uric acid stone formers, protein, and sodium intake must be restricted for cystine stone formers. Urine should be acidified for struvite and calcium phosphate stone prevention. Urine pH is of utmost importance to prevent stone formation. Patients need careful follow-up to make sure that the infections are cleared.

CONCLUSION:

Despite medical advancements in this century, the incidence of urolithiasis is increasing day by day. Many aspects of this disease are unclear. However, it is quite clear that Randall's plaque, renal cell injury, crystal retention, and various promoters and inhibitors are responsible for stone formation.

These targets are critical to examine and analyze, as each has its etiology. When these targets are achieved then it would be easy to design and utilize the drug

for each specific type and stage of stone, by targeting the specific area.

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