THE KIDNEY STONE

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***Abstract*: Kidney stone is a type of crystal concretion that builds up the kidneys. It is a growing public health problem affecting about 12% of the world's population. The most common type of kidney stone, calcium oxalate, is produced in Randall's plaque in the renal papillary and has a multifactorial etiology. Stone formation is a complex process that involves several physicochemical processes, such as super saturation, nucleation, growth, fusion, and storage of urine stone components within tube cells. The imbalance between the substances that attract or prevent the flow of urine controls these stages. It is also important to note that cellular injury promotes tissue retention in the renal papillary area. When renal epithelial cells are exposed to oxalate, protein kinase pathways activated by p38 mitogen trigger the signaling flow leading to apoptosis. There is currently no effective treatment or prevention of kidney stones. Therefore, research focused on controlling urolithias is with new drugs to better understand the mechanism of kidney stone development. As a result, the purpose of this review was to compile the latest information on kidney origin, pathophysiology, and prevention strategies.**

***Keywords*: Kidney stone, type of urolithiasis, mechanism.**

INTRODUCTION

Stones in the urinary tract (also called nephrolithiasis or urolithiasis) arise when the urine getsoverly supersaturated in a mineral, causing crystal formation, growth, aggregation, and retention within the kidneys.[1]

Mineral concretions in the renal calyces and pelvis (FIG. 1) that are seen free or attached to the renalpapillae are termed kidney stones (calculi). Nephrocalcinosis is the term for diffused renal parenchymal calcification.[2]

It's a widespread condition that affects approximately 12% of the population, with a recurrence rate of 70-81% in males and 47-60% in females. Urine contains chemicals that prevent the formation of crystals.[3]

If the stones are small enough, they will travel through the urinary tract unnoticed and exitthe body in the urine. Urinary stones up to 5 mm in diameter can usually be passed via the urinary tract.

However, stones larger than 7 mm in diameter nearly certainly necessitate surgical intervention.[4]

Urolithiasis affects people of all ages, from newborns to those over 70 years old. Men have a 2–4 times higher risk of stone development than women, which could be attributed to men's increased muscle mass, which increases testosterone's capability while reducing estrogen's capacity for stone formation. Furthermore, the male urinary tract is more complex than the female urinary tract.

Estrogen may also help prevent calcium stone development by keeping urine alkaline and increasingprotective citrate levels.[5]

Crystals of calcium oxalate, a high quantity of uric acid, and a lack of citrate in the body are all majorcauses of kidney stones. The cornerstone of renal stone prevention in adults with a low risk of recurrence is lifestyle changes, whereas citrate supplementation and medicines areindicated for patients with recurring stones.[6]

The production of crystals above their metastable limit is referred to as supersaturation.

Many variables contribute to etiopathogenesis, including genetics, poor nutrition, socioeconomic situations, environmental conditions, metabolic alterations, and anatomic and infectious factors.[7]

EPIDEMIOLOGY OF KIDNEY STONE

Kidney stone disease frequency and recurrence rates are rising worldwide[8], with few effective treatments available. Urolithiasis affects around 12% of the world's population at some point duringtheir lives.[9]

It affects people of all ages, sexes, and races[10, 11], but men between the ages of 20 and 49 aremore likely to be affected than women.[12]

If patients do not use metaphylaxis, secondary stone formations are projected to recur at arate of10–23% per year, 50% in 5–10 years, and 75% in 20 years.[13]

Although the incidence of nephrolithiasis is increasing among girls, the lifetime recurrence rate ishigher in males.[14]

As a result, preventive care is critical in the treatment of urolithiasis.

According to recent studies, the prevalence of urolithiasis has risen in both industrialized and developing countries during the last few decades. This developing trend is thought to be linked tolifestyle changes like lack of physical exercise and food habits[15–16] as well as globalwarming.[17]

Kidney stones afflict 1 in 11 people in the United States, and 600,000 Americans are believedtosuffer from urinary stones each year. Urinary stones are predicted to affect roughly 12% of the Indian population, with 50% of those who develop them losing kidney function.[18]

THE URINARY SYSTEM AND STONES-

The urine filtrate is generated in the glomerulus and then goes through the tubules, where reabsorption and secretions change the volume and content. The proximal tubules handle the majority of solute reabsorption, while the distal tubule and collecting ducts handle finer modifications to urine composition. The Henley loop concentrates urine, which is made up of 95 percent water, 2.5 percent urea, and 2.5 percent minerals, salts, hormones, and enzymes. Glucose, salt, chloride, and water, as well as important elements like amino acids, proteins, bicarbonate, calcium, phosphate, and potassium, are reabsorbed and returned to the bloodstream in the proximal tubules. The salt and acid-base balance of the blood is controlledin the distal tubule.[19] As shown in Figure 1, the position of stones might vary.

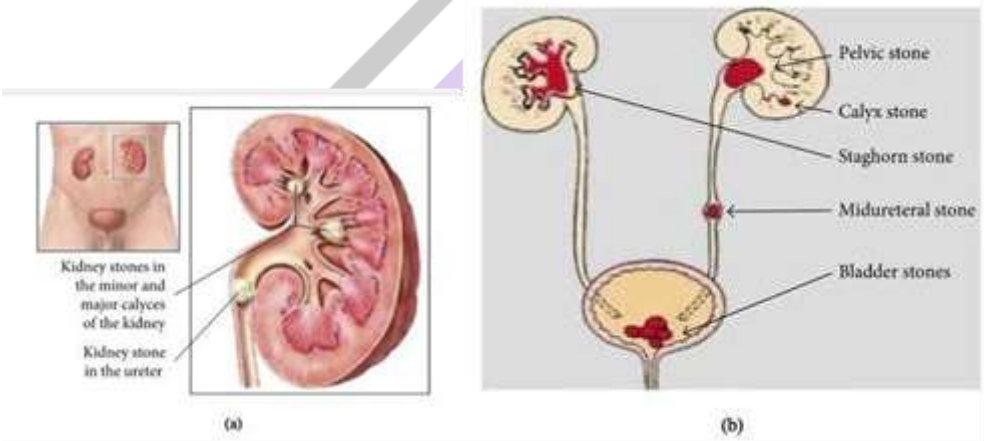

Figure 1: location of kidney stonein the urinary system. (a) Adopted from.[20] (b) Adopted from.[21]

TYPES OF KIDNEY STONES

1. Calcium crystals

The majority of kidney stones are calcium stones that have been combined with other substances. Oxalate, phosphate, or uric acid, in rare cases. Calcium One of the harmful outcomes is the production of oxalate crystals. Toxicity from ethylene glycol. Oxalate is a naturally occurring substance. A naturally occurring component in food a few fruits, fruits, nuts, and chocolates, have high oxalate content levels. Oxalate is also produced by the liver. Dietary influences, vitamin D supplementation, intestinal bypass surgery, and several metabolic conditions can cause an increasein blood sugar levels.

In urine, there is a high concentration of calcium or oxalate. All Radioactive calcium stones are opaque, as well as calcium oxalate Calcium phosphate stones can be black, grey, or whitish in color. Microscopically, calcium oxalate stones appear as 'envelopes.' Hyperparathyroidism and renal tubular acidosis are both linked to the production of calcium phosphate stones.[22]

2. Uric acid stone

Smooth, spherical, yellow-orange uric acid stones are almost radio graphically clear. Uric acid is responsible for about 5–10% of all kidney stones. Uric acid stones can form in people who don't drink enough fluids or lose too much fluid, those who eat a high-protein diet, diets high in purines, especially those containing meats and fish, and those who have gout. Obesity and certain genetic factors may also increase your risk of uric acid stones.[23]

3. Stones caused by the enzyme protease

This is the most recent stone type. The protease inhibitor indinavir sulfate is now widely used due tothe rising number of HIV-positive patients. This medicine may cause the production of stones in 4-12percent of people.[24]

4. Cystine Stones

Cystine stones are a type of stone. These stones are uncommon and occur in persons who have a genetic condition in which the kidneys discharge too many amino acids (cystinuria). Cystinuria causes people to excrete more than 600 mg of insoluble cystine each day. The stones are a roundedgreenish-yellow color, flecked with lustrous crystallites, and fairly radio- opaque.[25]

5. Silicate stones or drug-induced stones

These stones are quite uncommon. Loop diuretics, acetazolamide, and other drugs or natural products might cause these stones to develop. Laxatives, topiramate, zonisamide (when abused), triamterene, indinavir, ciprofloxacin, sulfa medicines ephedrine, guaifenesin, and silica-based products.[26]

MECHANISM OF STONE FORMATION

1. The physicochemical mechanism of kidney stone formation

The driving factor for intrarenal crystal precipitation is urinary supersaturation and crystallization, which is mostly caused by inherited or acquired illnesses that induce renal function impairment. Additionally, urine pH and specific concentrations of substance excess, such as CaOx, CaP, uric acids and urates, struvite, amino acids (cysteine), purines (2,8- dihydroxyadenine and xanthine), and drugs (e.g., atazanavir, amoxicillin, ceftriaxone), influence urinary supersaturation and crystallization.[27,28] Furthermore, crystal formation and multiple modulator chemicals have an impact on development. They are referred to as receptors, promoters, and inhibitors.

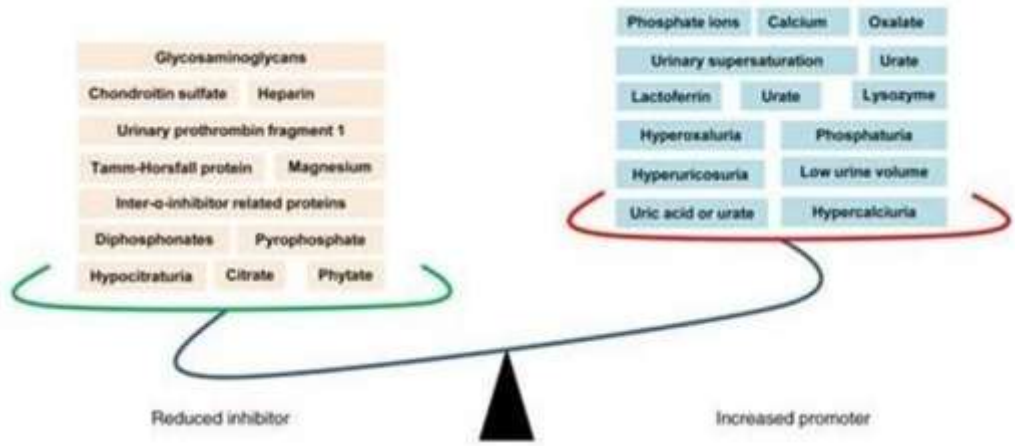

Figure 1: Physicochemical mechanisms of kidney stone formation.

Stone formation promoters

Crystal cell contact, which is acknowledged as the most significant pathway for crystal retention in kidneys, has been revealed to involve several receptors or receptor-like properties.[29,30]

CD44, nucleolin, hyaluronic (HA), heat shock protein 90 (HSP90)[32], Annexin II[33], and other proteins and glycosaminoglycan's OPN (osteopontin) has been reported to act as a stone breaker.[31,34]

The formation modulators, which have undergone a rigorous examination, earlier[35], Several molecular structures and components They also serve as receptors in crystal attachments, such as the lipid bilayer's phosphatidylserine component and the proteins with acidic side chains.[36]

Stone formation inhibitors

The presence of many inhibitors in normal urine reduces crystallization and inhibits crystal aggregation and/or adherence to tubular epithelial cells by acting both competitively and cooperatively.[37,38]

There are three types of inhibitors: anions, metallic cations, and macromolecules. At concentrations greater than 0.1 mm, anions such as citrate can effectively prevent crystal formation.[39,40] Citrate excretion was reduced in the majority of nephrolithiasis patients. Alkali supplements are commonly utilized to restore citrate excretion in hypocitraturia recurrent nephrolithiasis patients.[41,42]

Hydroxycitrate is a structural analogue of citrate that has been shown to have similar ability to form calcium structures to prevent crystallization (43,44). In acidic settings, metallic cations such as magnesium have been shown to limit crystal formation and coagulation, which is associated with citrate.[45-47]

The most powerful inhibitors of crystal formation are macromolecules. OPN, Tamm-Horsfall protein(THP), urine prothrombin fragment 1 (UPTF1), nephrocalcin (NC), and certain serum II subunits are all capable of inhibiting crystal development, aggregation, and/or adherence to tubular cells.[48,49,50]

2. Randall's plaque and the development of calcium oxalate stones

RPs are patches of subepithelial mineralized tissue at the papillary tip, enclosing the mouths of theBellini ducts containing CaP, initially postulated by Alexander Randall in 1937.[51,52] RP is made up of a mixture of tubules with calcified walls and tubules occluded by CaP plugs,according to scanning electron microscopy (SEM) analysis.[53]

RP is made up of CaP crystals mixed with an organic matrix rich in proteins and lipids, as well as membrane-bound vesicles or exosomes, collagen fibers, and other extracellular matrix components.[54]

3. The role of sex hormones in nephrolithiasis caused by calcium oxalate

Men have 23: 1[55,56] CaOx and prolithiasis higher than women, according to statistical analysis; however, the exact cause is unknown.

Previous studies have found that androgens improve urinary oxalate output, plasma oxalate concentration, and CaOx crystal deposition in the kidneys, while estrogens decrease.

In addition, increased androgen signaling may be a factor in linking sex to kidney stones.[56-59]

At the transcriptional level, androgen receptor (AR) signaling can directly increase hepatic glycolate oxidase[60] and epithelial kidney nicotinamide adenine dinucleotide phosphate oxidase (NADPH), subunit p22PHOX, to promote oxalate production, eventually leading to in the formation of kidney stones.[61] According to Peng et al.[62], testosterone contributes to the development of nephrolithiasis by inducing apoptosis and necrosis in renal tubular epithelial cells via the HIF1 / BNIP3 gene.

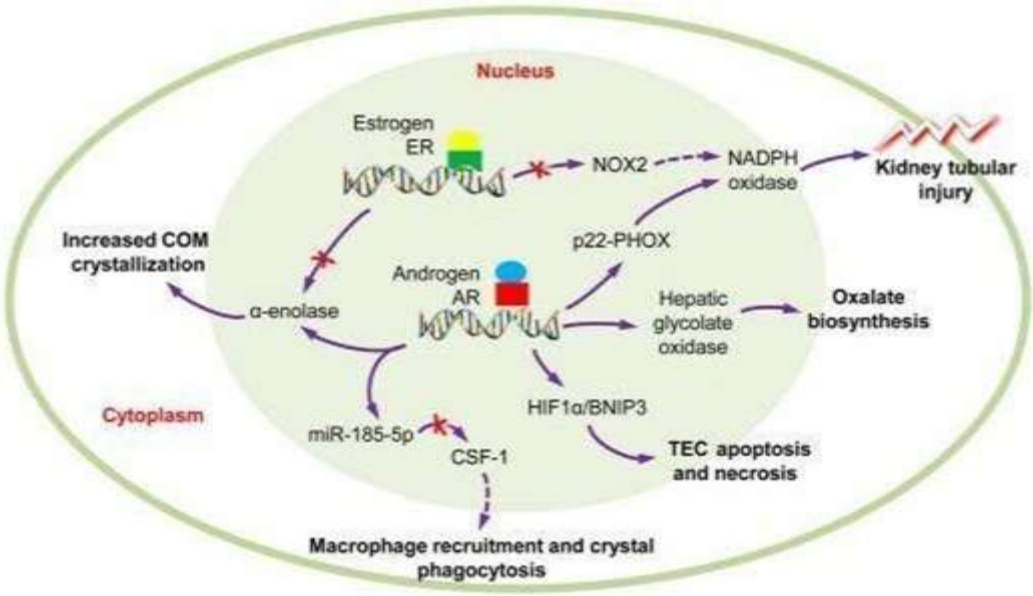

Figure 2: Role of sex hormones in calcium oxalate nephrolithiasis.

4. Role of the microbiome in stone formation

Due to their metabolic output and other contributions, microorganisms belonging to the human microbiome, including microbes of the kidney and urinary tract, are anticipated to have a dramaticeffect on urological health, both positive and negative, according to emerging research.[63]

Urease-producing bacteria

Proteus mirabilis, Klebsiella pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa, Providentia stuartii, Serratia, and Morganella morganii are all linked to the production and recurrence of struvite stones.

Urease is a bacterial enzyme that degrades urea and stimulates the creation of ammonia and carbondioxide, resulting in urine alkalinization and phosphate salt generation.[64,65]

Urinary acidification and urease inhibitors have been proposed and used to prevent and/or dissolve struvite stones and encrustations in patients with urea-degrading bacterial infection; however, theirlong-term usage is limited due to their ineffectiveness and toxicity.[66]

Non-urease generating bacteria, such as Escherichia coli and Enterococcus spp., have also beenshown to cause secondarily infected stones.[67, 68]

However, it's uncertain whether kidney stones form first and then become infected, or whether theyform as a result of an infection nidus that spreads stone formation. Nanobacteria are microorganisms that are smaller than bacteria (NB).

NB has been isolated from kidney stones for more than 30 years.[69-71], but the nature and mechanisms involved are unknown.

Ansari et al.[72] showed that cultured NB can infect individuals with apatite kidney stones and thattheir size varies between 60 and 160 nm.

Through self-proliferation, Kajander et al.[73] found that NB can adapt to growing in plain DMEM orRPMI1640.

In a study by Ciftçioglu et al.[74], it was discovered that NB.T was present in 70 of 72 (97.2%) kidneystones.

Figure 3. Role of urease-producing bacteria in stone formation. Fig.Role of nanobacteria in stone formation.

Figure. Role of oxalate-degrading bacteria in stone formation.

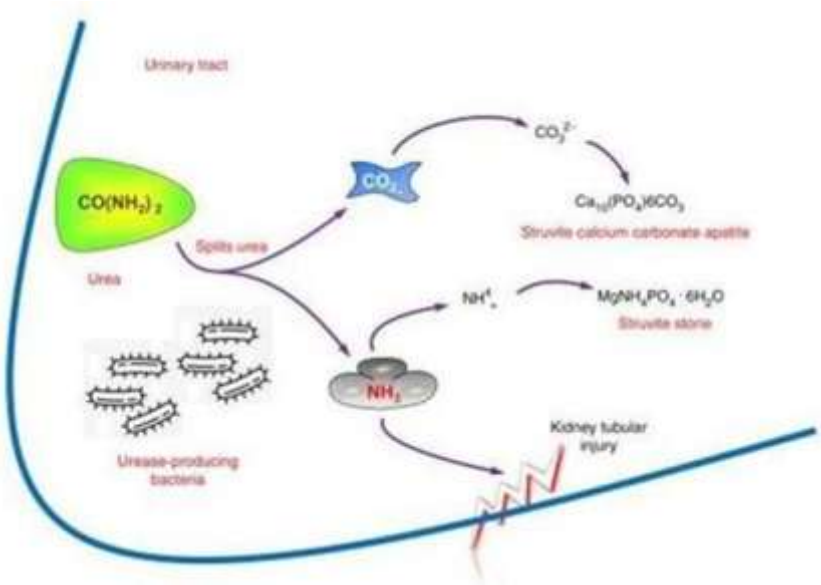

Figure 3: Role of urease-producing bacteria in stone formation.

PREVENTIVE OPTION FOR UROLITHIASIS

Causes of kidney stone production must be considered in order to effectively protect the stones.

In general, good diet control and drug use are important to avoid the first episodes of kidney stonesor subsequent episodes.

Dietary intervention to prevent kidney disease is an inexpensive public health system with far-reaching consequences for the community.

As a result, diet control is the most effective way to prevent urolithiasis.[75]

Patients should be advised to increase their water intake to keep urine out of at least 2 liters perday, regardless of basic etiology or stone therapy treatment.[76]

Drinking more fluids or water is a simple and important lifestyle change that can help you avoidstone sickness.

Drinking enough water reduces urinary incontinence and dissolves CaOx crystallization promoters.

Individual metabolic anomalies should be taken into account when making dietary recommendations.

Absorptive hyperoxaluria is treated with a low oxalate diet and supplemental calcium intake.[77]

A high sodium diet increases the chances of stone formation by reducing renal tubular calciumabsorption and increasing urine calcium.[78]

Animal protein inhibition is also recommended as animal proteins are high in acid due to their highamino acid composition.

As a result, a high-protein diet lowers the pH level of urine and citrate while increasing the excretionof calcium urine through bone rehydration.

As a result, if your urine is particularly acidic, you may need to eat less meat, fish, and poultry, andavoid foods that contain vitamin D.[79]

Instead, it is recommended to eat potassium-rich fruits and vegetables.[80]

CONCLUSION

Urolithiasis is becoming more common throughout the world, despite significant advancements inthe development of novel medicines for the treatment of urinary stones.

A lot of how kidney stones form is still a mystery.

Renal cell damage, crystal retention, cell apoptosis, Randall's plaque, and associated stone inhibitorsor promoters are all thought to play a part in the production of kidney stones.

These appear to be significant targets for creating a novel strategy for preventing kidney stonedisease as well as medications to treat kidney stones.

Additionally, identifying novel therapeutic targets based on molecular and cellular changes relatedto stone formation will aid in the development of better medications.

Furthermore, for stone removal drugs, a greater knowledge of the processes of urolithiasis associated with stone inhibitors or promoters would be crucial.

In addition, gaining a better understanding of the pathophysiology, etiology, and genetic basis of kidney stone production may hopefully lead to the development of new medications and techniquesto treat urolithiasis shortly.

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