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Review Article

The complex pathophysiology of urolithiasis (kidney stones) and the effect of combinational drugs

Meenakshi Malhotra*[1], Pooja Tandon[1], Kritika Wadhwa[1], Indu Melkani[2], Ajeet Pal Singh[3] and Amar Pal Singh[2]

[1] *Research Scholar, St. Soldier Institute of Pharmacy, Lidhran Campus, Behind NIT(R.E.C.), Jalandhar-Amritsar bypass NH-1 jalandhar-144011, Punjab, India.*

[2] *Associate professor, St. Soldier Institute of Pharmacy, Lidhran Campus, Behind NIT(R.E.C.), Jalandhar-Amritsar bypass NH-1 jalandhar-144011, Punjab, India.*

[3] *Academic Dean and Associate professor, St. Soldier Institute of Pharmacy, Lidhran Campus, Behind NIT(R.E.C.), Jalandhar-Amritsar bypass NH-1 jalandhar-144011, Punjab, India.*

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*Address for Correspondence:

Meenakshi Malhotra, Research Scholar, St. Soldier Institute of Pharmacy, Lidhran Campus, Behind NIT(R.E.C.), Jalandhar-Amritsar bypass NH-1 jalandhar-144011, Punjab, India.

Abstract

Body organs are very crucial when it comes to homeostatically maintaining them. If any changes occur in their function, it may lead to the development of diseases in the body. The kidney is one of the functionalised organs that is connected with the ureter and urinary bladder, which is basically the lower part of the body. The kidney priorly controls the volume of various body fluids, fluid osmolality, acid-base balance, various electrolyte concentrations, and the removal of toxins. Any dis-balance in the function of the kidney can generate a disease like renal calculi (kidney stone), chronic kidney disease (CKD), polycystic kidney disease (PKD), urinary tract infections (UTI), etc. Kidney stones (KS) are prevalent worldwide, affecting 15% of individuals. A stone arranged into various sizes may be micro, macro, and nano or found as mono or polycrystalline forms. The names of the two most common kidney stones, calcium and non-calcium stones (Uric acid stones, struvite stones, cysteine stones, and drug-induced KS), are determined primarily by their composition. Calcium stones are commonly found in individuals, approximately 80% of KS. This review provided recent details on kidney stone symptoms, etiology, psychophysiology, and management perspective.

Keywords: Kidney disease, calcium stone, renal calculi, chronic kidney disease, Polycystic kidney disease.

1. Introduction:

1.1 Kidneys and Urinary system:

In vertebrates, the kidneys are two reddish-brown, bean-shaped organs. Within the retroperitoneal space, they might be positioned to the left and right. Blood enters into the paired renal veins and leaves through the paired renal arteries. A ureter, a tube that transports expelled urine to the bladder, is attached to each kidney, as shown in Figure 1. The kidney's main functions include regulating the volume of different body fluids; fluid osmolality; acid-base balance; different electrolyte concentrations; and toxin elimination. One-fifth of the blood volume that enters the kidneys is filtered in the glomerulus, where filtering takes place. Amino acids, salt, bicarbonate, glucose, and solute-free water are a few examples of compounds that are reabsorbed. Materials like hydrogen, ammonium, potassium, and uric acid are examples of those secreted. Additionally, the kidneys carry out nephron-independent tasks. The structural and operational unit of the kidney is the nephron. A mouse kidney has roughly 12,500 nephrons, compared to approximately 1 million in an adult human kidney [1,2].

The elimination of nitrogenous waste from the body and the maintenance of homeostasis are the primary functions of the urinary system. The urine filtrate is created by the glomerulus and is passed into the tubules where it is changed in amount and content through reabsorption and secretion. While net change occurs in the distal tubules and collecting ducts, the majority of solutes are reabsorbed in the proximal convoluted tubules. The Henle loop is used to concentrate urine, which is mostly composed of water (95%) and urea (2.5%), as well as salts, hormones, and enzymes. Important vitamins, such as amino acids, proteins, bicarbonate, calcium, phosphate, and potassium, as well as glucose, salt, chloride, and water, are reabsorbed inside the proximal tubule and returned to the bloodstream. The distal tubule controls the blood's salt and acid-base stability [3].

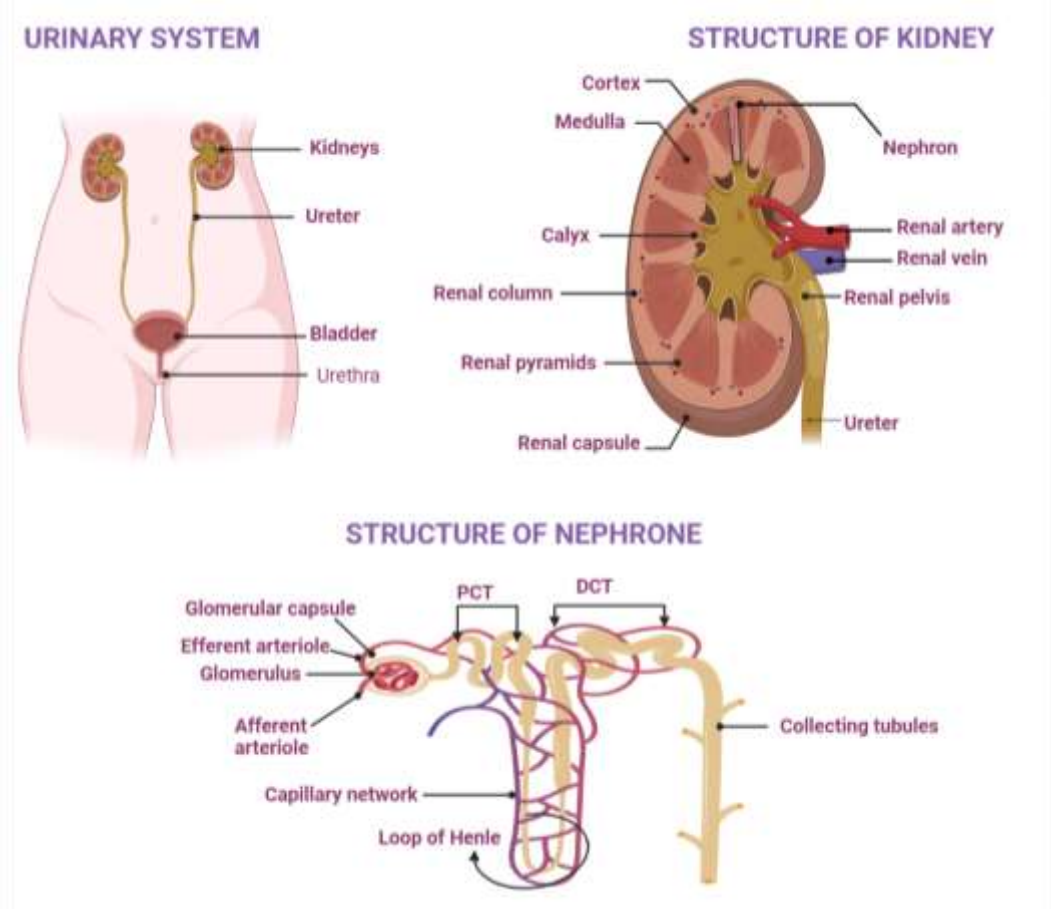

Figure 1: Structural Representation of the Nephrons, Kidneys, and Urinary System Anatomy: The kidneys, ureters, bladder, and urethra are all components of the urinary system[1].

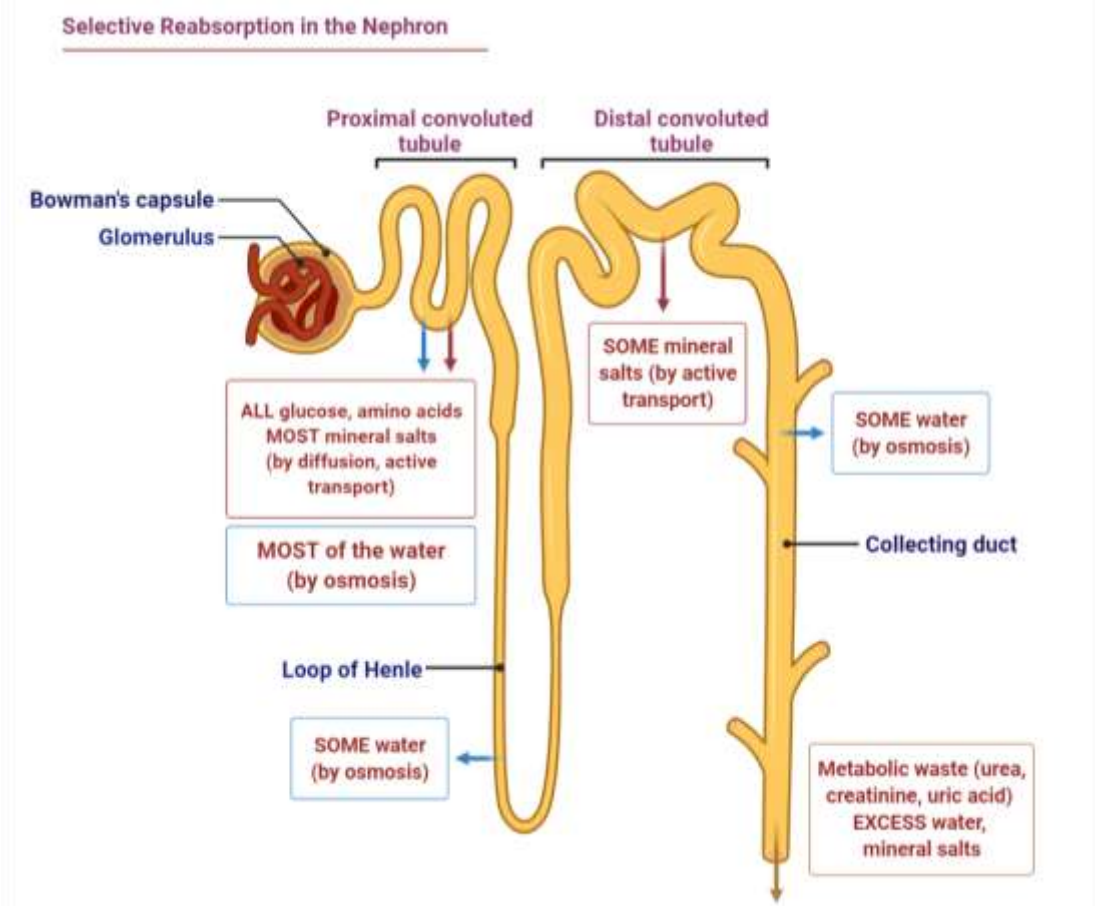

Figure 2: The Purpose of the Urinary System

The purpose of the urinary system is to filter blood and produce urine as a waste product. The kidneys, renal pelvis, ureters, bladder, and urethra are among the urinary system's organs. There are approximately one million nephrons, or filtering cells, in each kidney. The glomerulus and tubule are two filters found in each nephron. The glomerulus filters your blood, and the tubule restores nutrients to your blood and removes waste in the two-step process by which the nephrons function. The glomerulus filters the blood that the renal artery brings, and the PCT then receives it. The PCT of the nephron is where maximum reabsorption occurs. Essential molecules like glucose, proteins, amino acids, a significant number of electrolytes, and water are reabsorbed in the renal tubule's PCT. At the ascending loop of Henle, the electrolytes are reabsorbed, and as the filtrate travels to the ascending limb, it is diluted. However, this sector has a low reabsorption rate. The DCT involves the reabsorption of water and sodium ions. It therefore keeps the blood cells' pH and sodium-potassium levels stable. In a long, straight tube known as a collecting duct, H+ and K+ ions are secreted to keep the blood's electrolyte balance. Additionally, it is in this area where the most water is reabsorbable, leading to concentrated urine [2].

1.2 **Kidney stone disease** is One of the earliest disorders in urology is sometimes referred to as nephrolithiasis or urolithiasis. According to estimates, 1 to 15% of people will have kidney stones at some point in their lives, and nephrolithiasis is an increasingly common condition worldwide [4]. Stones in the kidney or urinary tract are crystalline, hard concretions that grow over time [5]. Nephrolithiasis is the word used to describe stone development in the kidney, whereas urolithiasis is used to describe stone formation in the urinary tract[6]. The passage of stones through the urinary tract can be painful because they are solid deposits of minerals and acid salts that adhere to one another in concentrated urine. Stones can develop in the ureter, bladder, kidney, and urethra. Stones can range in size from extremely large to extremely small, or they might appear as one stone or several stones. Because the male sex hormone testrosteone encourages stone formation and the female sex hormone oestrogen inhibits stone formation, the frequency of stone formation is three times higher in men than in women [7].

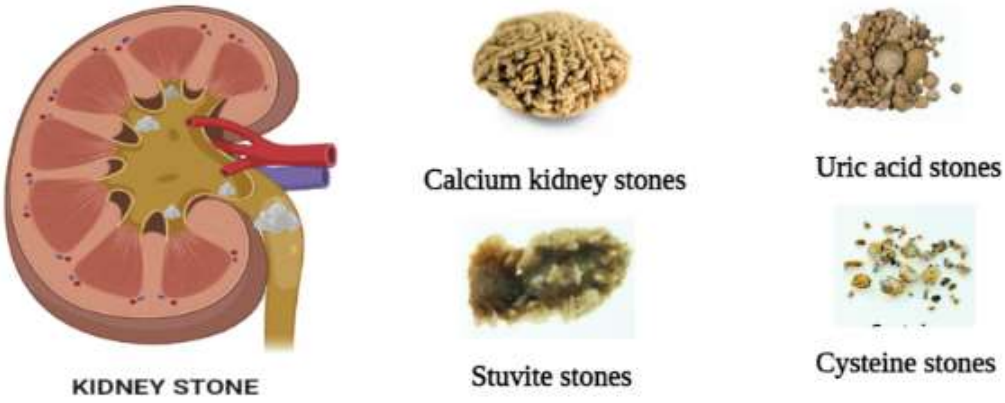

Figure 3: Kidney stones & Types of kidney stones [5].

1.3 Sites of stone formation: At least three routes lead to the stone formation, including: (1) in the renal

pelvis as a free solution, (2) as overgrowths on the sub urothelial papillary mineral deposits of Randall's plaque (RP), or (3) as an extension of an intratubular mineral plug [8].

2 Types:

Kidney stones can be either calcium or non-calcium, respectively (uric acid stones, struvite stones, cysteine stones). Notably, the names of the stones reflect the types of stone they are made of. The most common stone type worldwide is calcium stone.

2.1 Calcium stones: The most prevalent stones are calcium stones, which can be either alone or in conjunction with CaOx and CaP crystals. The majority of kidney stones are made of entirely or mostly calcium oxide, which can be either monohydrated or dehydrated. In 80–85% of all stones, calcium oxalate is the most common and uncommon form of stone. A daily diet high in oxalate, phosphate, and sodium plays a significant role in the development of calcium stones. Metabolic issues like hypercalciuria, hyperoxaluria, and hypocitraturia will result from this.

2.2 Uric acid stones: 8–10% of kidney stones worldwide are uric acid stones, which develop as a result of metabolic problems. Men are more likely than women to develop this form of stone. UA stone development is genetic, acquired, or a combination of both etiological causes. People with gout or gouty arthritis are more likely to develop uric acid stones.

2.3 Struvite stones: Infection stones, often referred to as struvite stones, make up 8% to 12% of all stones. Chronic urinary tract infections that raise the pH of the urine and promote bacterial growth are the root cause of these kinds of stones. These stones can be very large and can cause urinary tract infections. Women are more likely than men to get them.

2.4 Cystine stones: Cystine stones are quite infrequent and are brought on by cystinuria, a rare genetic anomaly. Increased urine cystine excretion results from a lack of cystine reabsorption [3,8].

2.5 Drug-induced stones: About 1% of all stones are made up of these stones. This kind of stone is brought on by medications including guaifenesin, triamterene, atazanavir, and sulfa medicines. Some lithogenic medicines or their metabolites may deposit in a nidus or on renal calculi that are already present, as in the case of people who take the protease inhibitors indinavir sulphate, a medication used to treat HIV infection and sensitive to developing kidney stones. Contrarily, these medications may cause calculi to form as a result of their

metabolic effects by interfering with the metabolism of CaOx and purines [3].

3. Sign and symptoms:

The signs and symptoms of urinary tract stones are as follows:

3.1 Urinary tract signs and symptoms:

- Renal colic - conventional colicky loin to groin or renal,
- Haematuria- gross or microscopic,
- Dysuria and strangury.

3.2 Systemic symptoms:

- Restless, writhing,
- Nausea,
- Vomiting,
- Fever,
- Cloudy or foul-smelling urine.

3.3 Asymptomatic symptoms:

- Incidental stones,
- Fluctuations in ache depth, with durations of pain lasting 20 to 60 mints,
- Chronic urge to urinate [7,9].

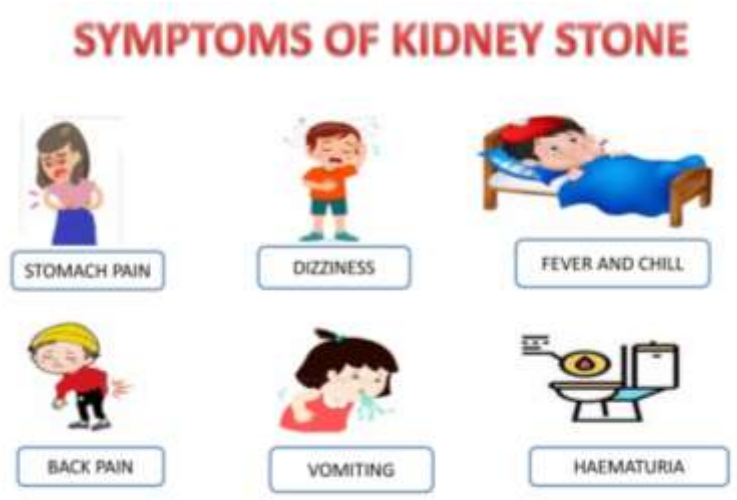

Figure 4: The clinical signs and symptoms of kidney stone disease (nephrolithiasis): The most prominent signs and symptoms include haematuria, back pain, nausea, dizziness, and vomiting.

4. Risk factors and causes for Calcium stones

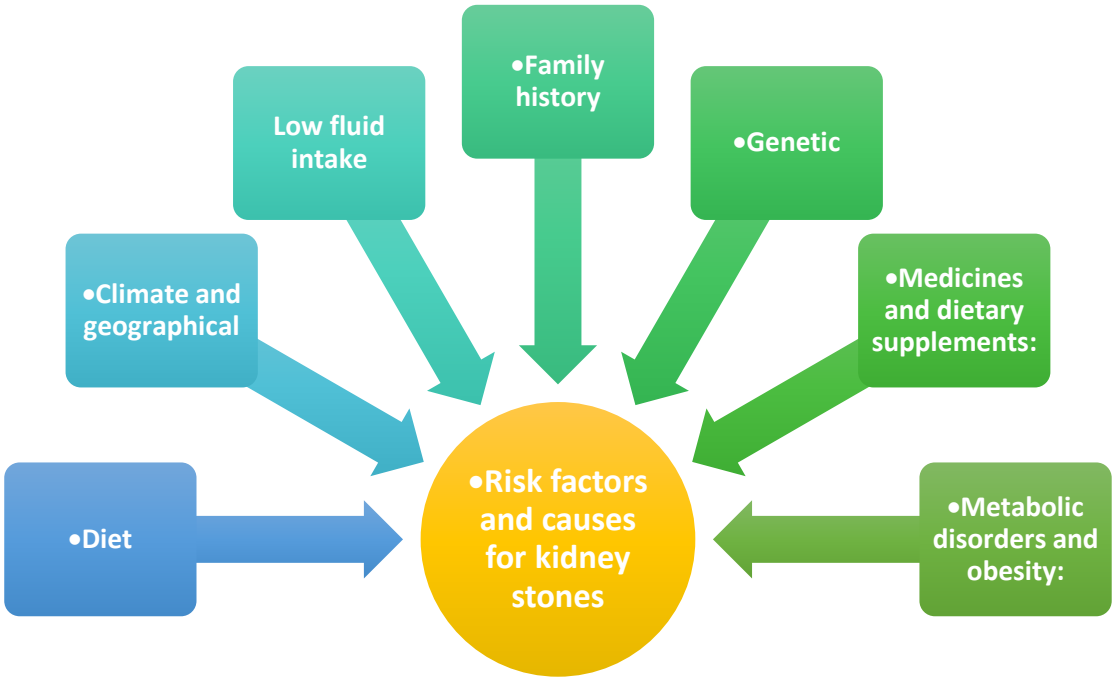

Figure 5: Various causes and risk factors of kidney stones[10].

4.1 Climate and geographical:

The prevalence of stone disease varies geographically, according to numerous epidemiological studies [11].

4.2 Diet:

The impact of diet on the prevalence of stone disease may be significant. Dietary components that have been linked to stone disease include animal protein, extra calcium, sodium, oxalate, and fruit juices. It has been established that consuming too much animal protein causes a decrease in urinary citrate and an increase in the excretion of calcium and uric acid. Additionally, a recent study found that individuals who get idiopathic calcium stones repeatedly have higher urinary oxalate excretion when they follow a diet high in animal protein [12].

4.3 Family history-

An increased risk of urinary stone problems is associated with a positive family history of urolithiasis. According to an epidemiological study, the frequency of stone disease includes a hereditary component. Environmental and nutritional factors have no bearing on this [12].

4.4 Genetic-

According to research, transporters and channels, ions, protons, and amino acids, the calcium sensing receptors (G-protein coupled receptor) signalling pathway, and the metabolic pathways for vitamin D, oxalate, cysteine, purines, and uric acid all play crucial roles in the aetiology of nephrolithiasis [13].

Table.1 Genes involved in hypercalciuria and stone formation, their renal expression and renal phenotypes.

S.NO.	Gene	Gene function	Renal tubular expression	Renal phenotype
1	DR	Vitamin D receptor	DCT, CD	Decreased calcium reabsorption.
2	CLCN5	Cl/H antiporter	PT, TAL, αIC	Inactivating mutations
3	CASR	Calcium sensing receptor	PT, MCD, TAL, DCT	Gain of function mutation
4	CLDN16	Tight junction protein	TAL, DCT	Hypercalciuria, magnesium-wasting
5	NPT2a/c	Sodium phosphate co-transporter	PT	Hypercalciuria, magnesium-wasting
6	TRPV5	Calcium selective transient receptor potential channel	DCT, connecting tubule	Hypercalciuria
7	sAC	Soluble adenylate cyclase/ bicarbonate exchanger	DCT, TAL, CD	Hypercalciuria
8	KLOTHO	Aging suppression protein/ regulator of calcium homeostasis	DCT	Hypercalciuria.

4.5 Low fluid intake-

The supersaturation of urine solutes, which results in urinary crystals that act as a nidus for stone development, is one of the main processes of stone formation. Poor urine excretion and stone development are caused by low fluid intake. Improved urine calcium concentration has been linked to the hotter summer months, which may also increase the risk of calcium stones. Maintaining enough hydration is crucial to preventing the formation of stones, with a daily urine output goal of more than 2-2.5 litres each day.

4.6 Medicines and dietary supplements:

People who take the protease inhibitor indinavir sulphate, a drug used to treat HIV infection and are susceptible to developing kidney stones, may experience deposits of some lithogenic medications or their metabolites in a nidus or on already existing renal calculi. Contrarily, these drugs may interfere with the metabolism of CaOx and purines, leading to calculi formation as a result of their metabolic [3]. Additionally, it has been demonstrated that consuming too much animal protein causes a decrease in urinary citrate, another factor in kidney stone disease, and an increase in the excretion of calcium and uric acid [12].

4.7 Metabolic disorders and obesity

Nephrolithiasis started to be linked to a higher body mass index. The primary metabolic risk factors for kidney stones include obesity, hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia shown in Figure. Nephrolithiasis has started to be linked to a higher body mass index. The primary metabolic risk factors for kidney stones include obesity, hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia, as shown in the figure 6.

5 Pathophysiology of calcium stones:

Calcium oxalate (CaOx), which makes up about 80% of calcium kidney stones, is also present in tiny amounts (15%), as is calcium phosphate (CaP). Low urine volume, hypercalciuria, hyperuricosuria, hypocitraturia, hypocitraturia, hyperoxaluria, and altered urine pH are some of the complex and varied pathophysiological pathways that lead to the development of calcium kidney stones [14]. A series of actions taking place inside the urinary tract leads to the production of stones. The imbalance between the promoters and inhibitors of urinary stone development is what starts the process. Oxidative stress is produced as a result of the promoter-inhibitor imbalance in stones. Inflammation and damage to the renal tissue are results of oxidative stress. The crystal nucleation takes place here. Additionally, when urine becomes oversaturated, crystals that can become kidney stones begin to accumulate, grow, and form renal calculi [15]. Dr. Randall discovered two areas of renal papillae calculus development in 1937. The principal location is found in the interstitial, more specifically inside the papillary tips that span the bends of the Henle loop. Calcium phosphate production in the interstitial is now understood to be the first stage. The deposits last longer as

more herbal compounds and crystal elements are accumulated. When in contact with urine, some of the calculi are degraded by the urothelium and ordinary plaque. The **fixed-particle mechanism is** this. At the tip of the collecting duct, inside the renal tubule, is the second site (duct of Bellini). When the precipitates are too heavy to avoid, or when certain conditions arise, retention occurs Retention occurs when the precipitates are too large to avoid or when they stick to damaged cells, presumably due to oxidative pressure. This idea is referred to as the **free-particle mechanism** [16–18].

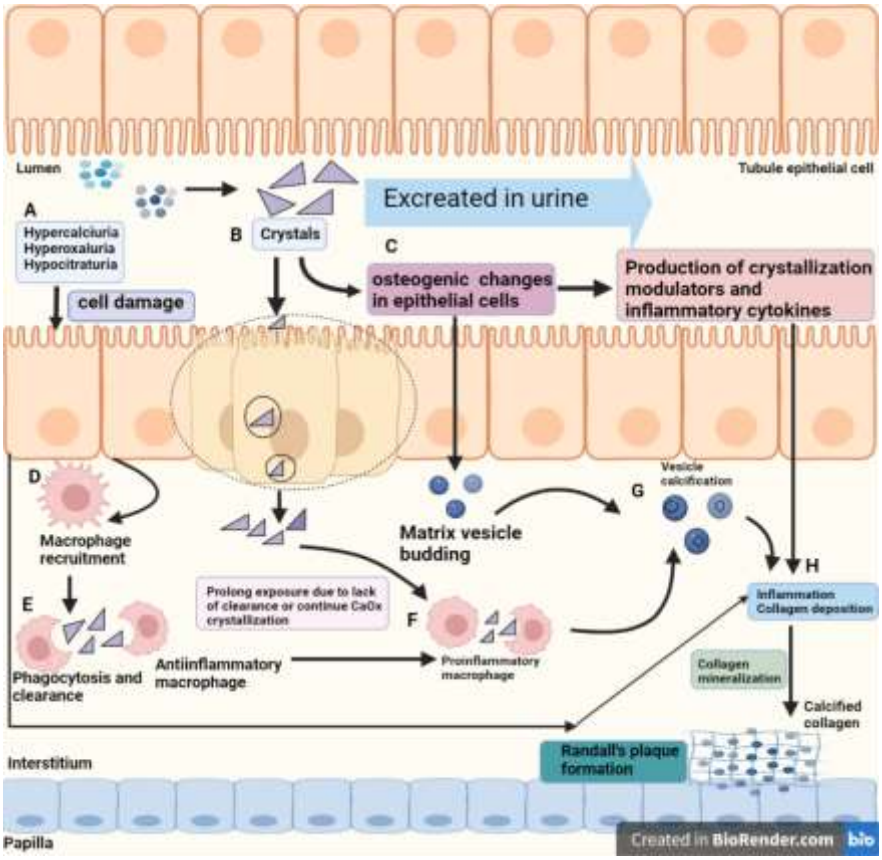

Figure 6: Stone Formation's Pathophysiological Mechanism (A) Renal cell injury is caused by a number of metabolic risk factors, including hyperoxaluria, hypercalciuria, and hypocitraturia. (B) A decrease in urine flow, a shift in urine pH, or an increase in stone-promoters are the three factors that lead to crystal formation. If any formed crystals are left after urine excretion, they will bind to epithelial cells and produce toxicity, physical harm, or receptor activation. This encourages osteogenic changes, an inflammatory response, and mineralization. (D) Attached crystals can interface with tissue macrophages and enter interstitial areas to begin endocytosis. That starts cell death and damage. (E) crystals are destroyed and phagocytosed by anti-inflammatory macrophages (F) Prolonged contact with crystals can turn normally anti-inflammatory macrophages pro-inflammatory. (G) Calcification and collagen deposition are triggered by an increase in proinflammatory macrophages. (H) Mineralization and Randall's plaque development are brought on by collagen deposition[19].

6 Process of stone formation:

The process of stone formation involves numerous steps describe below:

Step 1: Imbalance of urinary stone promoters-inhibitors

- **Urinary stone promoters:**

Through a variety of ways, promoters can speed up the crystallisation of stone components or their boom. An increase in the attention of the reactants might raise the saturation. The development of heterogeneous nucleating materials may be induced by an excessively low or high urine pH. Promoters can use a variety of processes to aid in the crystallisation of stone components or their growth. An increase in reactant concentration may result in a higher saturation. The production product may be diminished by compounds in the urine, but it will also be reduced by the loss of endogenous inhibitors, by resistance to their actions by producing faults in their structure, or by the presence of other interfering substances. The development of stones could be due to an increase in promoters. The main factors that encourage the development of stones include phosphate ions, calcium, oxalate, urinary supersaturation, urate, lactoferrin, lysozyme, hyperoxaluria, phosphaturia, hyperuricosuria, low urine volume, uric acid, and hypercalciuria [10,20].

- **Urine stone inhibitors:**

Small organic anions like citrate, small inorganic anions like pyrophosphates, multivalent steel cations like magnesium, or macromolecules like osteopontin and Tamm-Horsfall protein are the four different types of inhibitors found in urine. The compounds known as inhibitors have the potential to prevent the onset of supersaturation, nucleation, crystal development, rate of aggregation, and any other processes necessary for the creation of stones. Small organic anions like citrate, small inorganic anions like pyrophosphate, multivalent metallic cations like magnesium, and macromolecules like glycosaminoglycans, chrondrotion, sulphate, heparin, urinary

prothrombin fragment-1, Tamm-Horsefall protein, inter-inhibitor related proteins, diphosphonates, phytate, etc. are all inhibitors of the formation of stones. These elements' abnormal function and concentration might encourage the stone's development [10,20].

Step 2: Urine supersaturation:

All phase transitions are pushed by supersaturation, which is often approximated for such salts by the ratio of their concentration within the urine to their solubility. Stones are the outcome of a phase change in which dissolved salts condense into solids. Rapid urine supersaturation and the subsequent deposition of crystalline debris lead to the development of renal stones. The force that causes crystallisation in liquids like urine is supersaturation. When a salt is given to a solvent, it dissolves there up to a certain point, after which no further dissolving is possible [21].

Step 3: Oxidative stress:

The production of stones is signalled by an increase in ROS (Reactive Oxygen Species), which also damages cells. In the presence of angiotensin II, NADPH oxidase is a major generator of ROS in the kidney [22]. Crystal aggregation and retention, crucial processes in kidney stone development, are closely linked to free radical activity in vivo. The formation of calcium oxalate (CaOx) crystals, the most frequently diagnosed kind of urinary tract stone, results in the upregulation of renin and the production of angiotensin II, which activates NADPH oxidase and intensifies ROS production. Then, ROS activates transcription factors via the P38 mitogen-activated protein kinase (-MAPK)/JNK, activated protein-1 (AP-1), nuclear component kappa-mild chain-enhancer of activated B cells (NF-B), and boom factors such as TGF, Runt-related transcription factor-2 (RUNX-2), and obsterix, as well as other signalling pathways. In actuality, ROS-precipitated transcription activation affects inflammatory responses. ROS-stimulated NF-kB (CRP). Cell damage and inflammation could result from this. Then, in a vicious cycle process, those substances may also activate NADPH oxidase and perhaps drive ROS production, which can also compromise endothelial function [23,24].

Step 4: Crystal Nucleation:

In a supersaturated solution, nucleation is the initial phase of crystallisation, or the transition from a liquid to a stable phase. This process starts with a loose cluster of aggregated stone salts in solution that can be enlarged by being supplemented with more recent additions or clusters. The fundamental crystals that don't disintegrate and have a distinctive lattice pattern are shaped by nuclei. Nuclei in urine often form on current surfaces in a process known as heterogeneous nucleation. Urine can contain epithelial cells, urinary elements, RBCs, and other crystals that can function as nucleating centres. In comparison to homogeneous nucleation, heterogeneous nucleation requires substantially less saturation. A nucleus can begin to develop as soon as it is formed, and essentially, if it is anchored, crystallisation can occur at lower chemical pressures than needed for the initial nucleus to form. By providing ingredients for heterogeneous nucleation, cellular injury to the renal tubules can encourage the crystallisation of CaOx. Numerous membrane vesicles, which have been shown to be reliable calcium crystal nucleators, are produced during in vitro cell breakdown after renal tubular cellular damage [21].

Step 5: Crystal Growth:

Crystal growth comes next in the production of stones after nucleation. Crystal growth is a small, challenging lump of stone formed when crystals in urine stick together. Aggregation is the process used to grow stones. Numerous proteins have different functions in crystallisation in nephrolithiasis urinary stone matrix protein modulators [3].

Step 6: Crystal Aggregation:

A small, challenging mass of a crystal in solution binds together through the process of crystal aggregation to form a larger stone. Aggregation describes it. Crystal aggregation is regarded as the most crucial stage in the production of stones [3].

Step 7: Crystal-cell interaction:

The bonding of growing crystals with the renal tubule lining of epithelial cells is referred to as Crystal retention or "crystal-cell interaction". Renal tubular epithelial cells have been damaged in people with hyperoxaluria as a result of exposure to high oxalate concentrations or sharp calcium oxalate monohydrate (COM) crystals. Crystals travel from the basolateral side of cells to the basement membrane, where they interact with cells. Crystals may then be taken up by cells and attached to the kidneys' basement membrane. A crucial first event in the development of nephrolithiasis may be the interaction of COM crystals with the surface of renal epithelial cells. A doubled retention force between the crystal and damaged renal tubule epithelial cells promotes CaOx crystallisation. The majority of crystals attached to epithelial cells are excreted in urine after not being digested by internal cells called macrophages and/or lysosomes. After renal tubular cells are damaged, cellular breakdown creates a number of membrane vesicles that can act as calcium crystal nucleators. Renal prothrombin fragment-1 and other anionic proteins, as well as other chemicals, are released by injured cells and contribute to the formation of COM crystals [3].

Step 8: Endocytosis of CaOx Crystals:

The earliest stage of kidney stone production is endocytosis, or the engulfment of crystals by renal tubular cells. According to research on the interactions between tissue culture crystals and cells, COM crystals quickly cling to microvilli on the cell surface before being internally absorbed. Glycosaminoglycans, glycoproteins, and citrate are polyanion compounds found in tubular fluid and urine that may coat crystals and prevent COM crystals from adhering to cell membranes. In the biological process of stone formation, Tamm-Horsfall glycoproteins (THP) have a dual role. Cells can either be carried to the interstitium by cells or be endocytosed by them. It is advised that damaged cells enlarge a nidus, which encourages the retention of particles on the renal papillary surface [3].

Step 9: Cell injury and Apoptosis:

High oxalate or CaOx concentrations injure epithelial cells, which is a risk factor for the development of stones. In addition to causing stone development, apoptosis at the level of renal tubular cells may also result in cellular death and post-apoptotic necrosis, which may halt calcium crystal growth and aggregation. In vitro analysis of MDCK cells exposed to oxalate ions has confirmed this fact. However, it should be highlighted that not all cells respond to oxalate damage. This might be the case because changes in gene expression should first protect from apoptosis and then inhibit lithiasis. Future research is necessary to identify new molecular targets for kidney stone formation, as these data make clear [3].

Step 10: Immune response to urinary crystals:

The primary immune response deviations identified in kidney stone illness are macrophage accumulation, macrophage-related inflammation, and anti-inflammation, which are

commonly believed to play a crucial role in renal CaOx crystal formation [25]. Beginning with the interaction of CD44 with OPN and fibronectin (FN), which may be up-regulated in renal tubular cells, the recruited macrophages should support the formation of COM crystals [26].

Second, it has been demonstrated that macrophages release a variety of mediators that lead to renal interstitial infection through traditional secretory channels [4,27], Interleukin-8, macrophage inhibitory protein-1 (MIP-1), and monocyte chemo attractant protein-1 (MCAP-1) are three examples of these proteins (IL-8) [27]. As a result, these chemokines promote the migration of a variety of immune cells into the inflammatory site, including monocytes, macrophages, neutrophils, dendritic cells, and T-cells [28,29].

According to mounting evidence, M1/M2-macrophage differentiation is crucial for the development of renal CaOx crystals. CaOx inflammatory damage could reduce through crystal phagocytosis by M2-macrophages, whereas M1-macrophages are essential for CaOx stone formation. [4,26,29].

7 Diagnosis:

Patients History:

Patient's medical history should be taken into consideration [30] shown in table 5.

Table 2: Various conditions and their causes

S.no.	CONDITION	CAUSES
1.	Presence of systemic illness	Primary hyperparathyroidism Renal tubular acidosis Cystinuria Gout Diabetes mellitus Inflammatory bowel disease Renal insufficiency Sarcoidosis Medullary sponge kidney
2.	Anatomical features	Presence of horseshoe kidney Previous urinary diversion Obstruction of the ureteropelvic junction Solitary kidney Previous renal or ureteral surgery
3.	Previous kidney disease	History of urinary tract infection or pyelonephritis, or both Family history of urolithiasis Detailed history of previous stone events
4.	Treatment	Stone analysis Carbonic anhydrase inhibitors (topiramate)
5.	Drugs that affect stone disease	Ephedrine Guaifenesin Calcium with vitamin D Triamterene Indinavir or sulfadiazine

Laboratory Evaluation:

- **Blood Test** - CBC (complete blood count) number for the presence of an elevated white blood cell count (Neutrophilia), and so on.
- **Urine Test** - Microscopic study of urine: shows proteins, RBCs, microorganism, cell casts and crystals.
- **The 24-hour urine Test** - measures general daily urinary excretion, magnesium, sodium, uric acid, citrate, calcium, oxalate and phosphate.

Other:

There are several alternatives, including an intravenous pyelogram (IVP), a computed tomography (CT) scan, and an X-ray renal ultrasonography [9].

8. Prevention & Treatment of Kidney stone disease:

8.1 Preventive measurements: The best strategy to reduce urine supersaturation and stop stones from returning is to increased fluid intake, balance diet, and citrate supplement [31].

8.2 Treatment approaches: The symptoms, size, and placement of the stone inside the kidneys all affect how kidney stones are treated. Stones small in size should be eliminated using pharmacological therapies and prophylactic measures. A surgical method should be used to remove big stones.

- **Surgical procedures**: A variety of surgical techniques, including ureteroscopy (URS), extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), and open or closed stone removal procedures, have been advised for the removal of stones larger than 5 mm in size. The size, position, and shape of the stones will determine which surgical treatment is chosen [7].
- **Herbal therapy:** There are numerous commercially available herbal preparations for treating kidney stones. Cystone (Himalaya Drug Company, India), Calcuri (Charak Pharmaceuticals, Bombay, India), Uriflush (Inti Sumatera Global, Indonesia), Uriflow (Discovery Herbs, USA), and Chandraprabha bati (Baidyanath, India) are marketed as composite herbal and Ayurvedic formulations that have been successfully used in clinical trials to dissolve urinary stones in the kidney and bladder. A composite herbal composition called Trinapanchamool, made up of the herbs *Desmostachya bipinnata, Saccharum officinarum, Saccharum nunja, Saccharum spontaneum*, and *Imperata cylindrica*, was found to be effective both as a preventative and a curative in pharmacological and clinical investigations [32].
- **Drug therapy:** Renal colic is treated with steroids and painkillers. Diuretics are used to reduce kidney stones and produce more urine. The choice of drug is depending upon the type and cause of the kidney stones. In Table 3, various classes of drugs used in the treatment of kidney stones are mentioned.

Table 3: Various drugs used to treat different types of conditions in kidney stones with their doses and side effects [33].

S.no.	Type of Kidney stone (KS) disease	Aetiology	Pharmacological Treatment	Dose	Side effects
1.	Calcium KS disease	Hypercalciuria	drochlorothiazide	50mg/d	Hypokalemia
			lorthalidone	25-50 mg/d	Glucose tolerance
			iloride	5mg/d	Hypomagnesemia
			lapamide	1.2-2.5mg/d	Hypertriglyceridemia
		Hyperuricosuria	opurinol	100-300mg/d	Rare or severe hypersensitivity
		Hypocitraturia	kali treatment	30-60mEq/d	Safer
		Hyperoxaluria	kali treatment	30-60mEq/d	Safer
			ridoxine	25-50mg/d	
2.	Non-Calcium KS disease	Uric acid stones	kali treatment	30-60mEq/d	Safer
			opurinol	100-300mg/d	Rare or severe hypersensitivity
		Cystine stone	kali treatment	30-60mEq/d	Safer
			Penicillamine	1000-2000 mg/d	enicillamine and α-mercaptopropionylglycine can result in arthralgia, leukopenia, thrombocytopenia, and proteinuria in addition to causing nausea, vomiting, diarrhoea, fever, skin rashes, and lupus-like syndrome.
			α-Mercaptopropionylglycine	400-1200mg/d	d-penicillamine often causes more serious side effects than α-mercaptopropionylglycine.
		Infectious stones	Acetohydroxamic acid	10-15 mg/kg/d	Only ineffectively removed infectious stones should be surgically removed, then the infection should be treated with antibiotics. Severe side effects of acetohydroxamic acid include intractable headache, hemolytic anemia, and thrombophlebitis.

- **Combination of therapies used to treat KS disease:** Combinational therapy is required to treat these aspects since kidney stones have complex pathophysiology and are brought on by a range of causes. Expulsion therapy is used in acute nephrolithiasis for the expulsion of stones throughout the body, and NSAIDs are mainly used to reduce pain and inflammation associated with stone formation. The primary agents are calcium channel blockers, steroids, phosphodiesterase-5 inhibitors, NSAIDs, and -adrenergic blockers. Diuretic therapy increases the renal fluid output and stone passage and elimination [32]. Administration of myorelaxing capsules (prifinium bromide, nociverine, flavoxate, fumariae herba) is rare nowadays. Although they counteract ureteral muscle ache and spasm, they inhibit ureteral peristalsis and, for that reason, impede stone advancement alongside the ureter. Edema, mucosal infection, or ureteral spasm are treated by the use of steroids. As they stabilise neutrophil lisosomes and inhibit prostaglandin launch, they reduce neighbourhood edema and exert a local analgesic impact [34].

9. Conclusion:

In this review article, the concepts of the epidemiology, types, clinical manifestations, causes, pathophysiology, steps involved in stone formation, diagnosis, prevention, and treatment of nephrolithiasis are discussed. It concludes that calcium stones are the most common type of kidney stone worldwide. The pathogenesis of renal calculi is complex, involving physicochemical, urine super saturation, and kidney stone related metabolic risk factors, receptors, promoters, and inhibitors, as well as investigations into the roles of immune response, microbiome, and sex hormones in stone formation and development. Preventive measurements to reduce the recurrence of stone formation include lifestyle modification, citrate supplements, and medication. These measurements are also used in acute nephrolithiasis. Treatment of kidney stones depends upon the size, location, and type of stones. Different surgical procedures have been recommended for stone removal greater than 5 mm, like Ureteroscopy (URS), Extracorporeal Shock Wave Lithotripsy (ESWL), Percutaneous Nephrolithotomy (PCNL), and open or closed stone removal procedures. The selection of surgical procedure depends upon the size, location, and shape of the stones. Pharmacological treatments are given for recurrent stone formation. This type of treatment is given for severe nephrolithiasis conditions. Medical therapies for primary expulsion of renal and ureteric stones, especially with the use of alpha-blockers and calcium channel blockers, have been shown to be effective.

10. Future perspectives:

The pathophysiology of kidney stone disease cannot be fully explained by crystallisation strategies alone. However, due to modern barriers in research, there are still a few regions in kidney stone formation that remain poorly understood and have not been mentioned here. In addition, comprehensive studies are necessary to similarly elucidate the mechanisms of the microbiome and immune reaction in kidney stone formation in order to broaden novel prophylactic and healing strategies.

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Conflict of Interest:

No conflict of Interest.

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