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NEPHROLITHIASIS: AN UPDATE ON CURRENT CONCEPTS

Shafiya Begum[1], Mohammed Madani[*1], Dr. Mohsina Hassan[2]

[1]Pharm. D student, Nizam Institute of Pharmacy, Deskhmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India. [2]Pharm. D, Assistant Professor, Department of Pharmacy Practice, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

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Abstract:

Nephrolithiasis is a solid crystal aggregation formed in the kidneys from dietary minerals in the urine. It can be caused by both environmental and metabolic factors. A large number of people around the world are suffering from this disease. The lifetime prevalence of nephrolithiasis is approximately 10% for men and 5% for women and more than $2billion is spent on its treatment each year. Calcium, Uric acid, struvite, cystine and drug-induced stones are the types of stones in nephrolithiasis. Approximately 75% of the stones are calcium based, 10% uric acid, 10% struvite and less than 1% accounts for cysteine and drug induced stones. The sequence of events that triggers the formation of stones can be classified into four stages namely – Nucleation, Growth, Aggregation and Retention. Nephrolithiasis is caused due to multiple risk factors. Although risk factors do not have a direct cause of the disease, but in some way or the other they are associated with it. The management of nephrolithiasis needs to be individualized. Clinical presentation, proper history and laboratory tests help to determine whether urgent surgical/medical treatment is needed. The aim of this review is to provide compiled up-to-date information on nephrolithiasis, its types, pathophysiology, risk factors, clinical manifestations and preventive approaches, including treatment.

Keywords: *Nephrolithiasis, Supersaturation, Nidi, Nidus, Acetohydroxamic Acid, Tiopronin, Percutaneous Nephrolithotomy.*

Corresponding author:

Mohammed Madani,

Pharm. D student, Nizam Institute of Pharmacy, Deskhmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India. E-mail: mohammedmadaniofficial@gmail.com.

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INTRODUCTION:

Nephrolithiasis or Renal Calculi is a solid crystal aggregation formed in the kidneys from dietary minerals in the urine [1]. It is caused due to a disruption in the balance between the solubility and the precipitation of salts in the kidneys and the urinary tract [2]. The term urolithiasis is used when stone is located in the urinary tract and if the stones are located in the ureters, it is referred as ureterolithiasis [1]. It can be caused by both environmental and metabolic factors [3]. Two major reasons may be responsible for kidney stones, rise in obesity, metabolic syndrome, diabetes and hypertension being the first and climate change being the second [4].

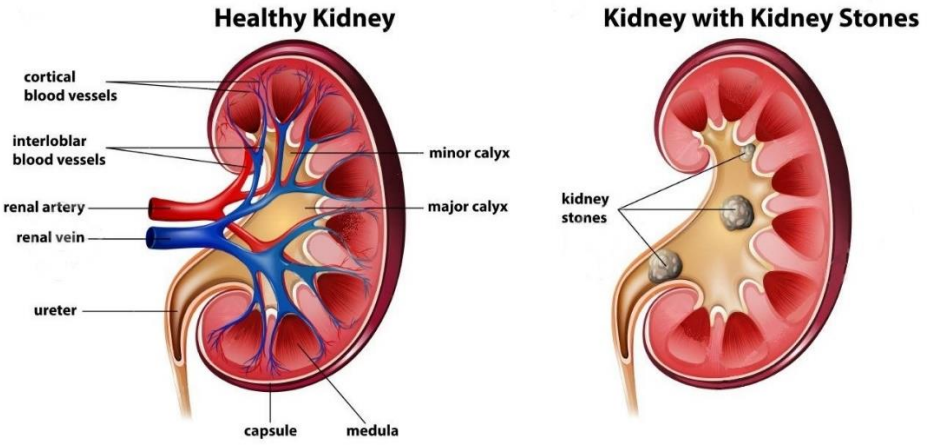

Figure 1: Difference between a healthy kidney and a kidney with stones [5]

Mankind has been afflicted with urinary stones since the ages of 4000 B.C [2]. Nephrolithiasis is a distressing chronic condition that is becoming common throughout the world [6]. Within urinary tract disorders, kidney stones are a major cause of morbidity [7]. Kidney calculus has become pandemic [8]. A large number of people around the world are suffering from kidney stones [3]. Excruciating, intermittent pain that radiates from the flank to the groin or to the genital area and to the inner thigh is the hallmark of stones that obstruct the urethra or renal pelvis. This particular type of pain, known as renal colic, is often described as one of the strongest pain sensations known [1]. Researchers found that Stone Formers had a 60 percent higher risk of developing chronic kidney disease (CKD) and a 40 percent higher risk of developing end-stage renal disease (ESRD), the most severe form of CKD [3].

Epidemiology:

Globally, the prevalence and recurrence of kidney stone disease are increasing [9]. The lifetime prevalence of symptomatic nephrolithiasis is approximately 10% for men and 5% for women, and more than $2 billion is spent on treatment each year [10]. It affects all ages, sexes and races [9], but they are quite common and usually affect people between 30 and 60 years of age [3]. Kidney stones are most common in males than in females between 20-49 years of age. The rate of recurrence in males is lower, although the incidence of nephrolithiasis in females is rising [9]. Without any medical treatment, the risk of recurrence is more than 50 percent over 10 years [8].

Structure of The Urinary System:

The urinary system is the primary excretory organ and consists of the following structures:

- Two kidneys which secretes the urine.
- Two ureters which carries the urine from the kidneys to the urinary bladder.
- The urinary bladder which gathers and stores the urine.
- The urethra through which the urine leaves the body [11].

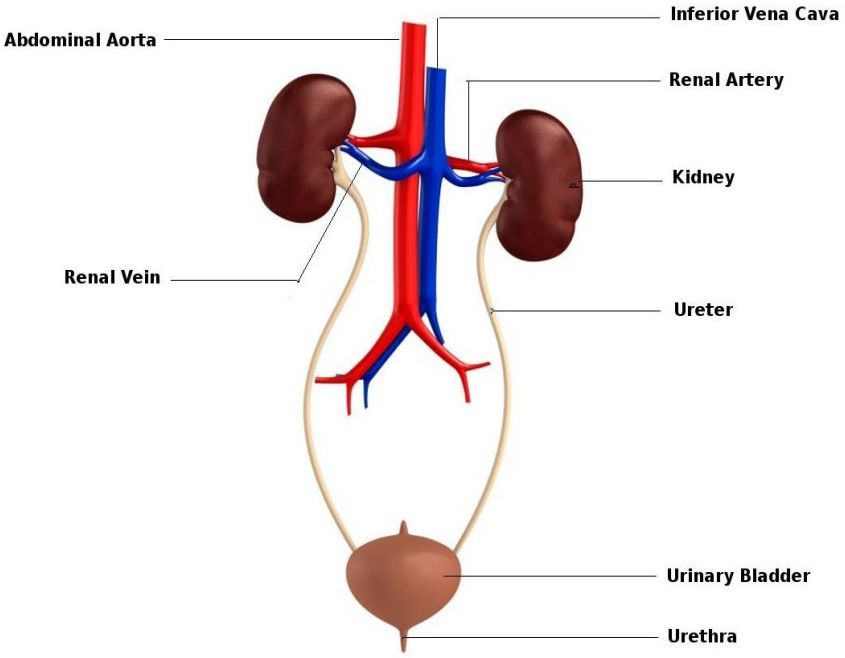

Figure 2: Urinary System diagram [12]

Kidneys:

The paired kidneys are reddish, kidney bean shaped organs [13] located between the points of the T12 vertebra and the L3 vertebra on the posterior abdominal wall. It is retro peritoneal in position [14]. Usually the right kidney is slightly lower than the left, possibly due to the large region of the liver [11].

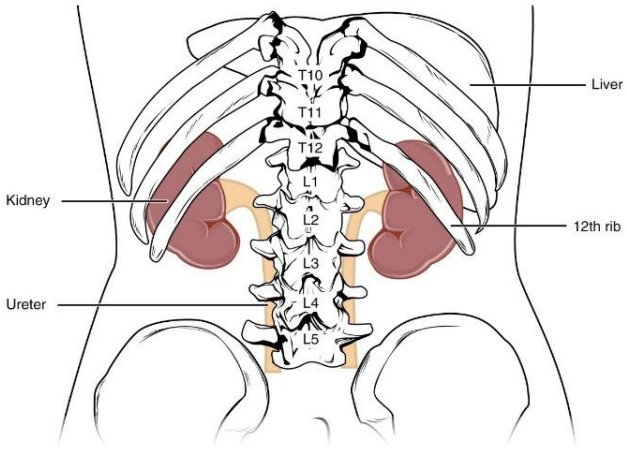

Figure 3: Kidneys. (The kidneys are slightly protected by the ribs) [15]

External Anatomy:

The typical adult kidney is 10-12 cm long, 5-7 cm wide and 3 cm thick and has a density of 135-150 g and is covered by three layers of tissue [13]. They are partially protected by a fibrous renal membrane made up of thick, irregular connective tissue which helps to keep their shape and protect them. The middle layer is a shock-absorbing layer of adipose tissue called a renal fat pad [15] that, in turn, is protected by a tough renal fascia that attaches the kidneys to the surrounding structures and to the abdominal wall [13].

The adrenal gland is on the upper side of each kidney [13], two yellowish pyramidal bodies that protect the upper poles of the kidneys. This consists of a superficial cortex and a deep medulla [14]. Adrenal cortex directly affects renal function through the

development of the hormone aldosterone to promote sodium reabsorption [15].

Internal Anatomy:
The anterior portion of the kidney contains an external region called the renal cortex and an internal area called the medulla [15]. The renal medulla consists of several cone-shaped kidney pyramids, the apex of which is called renal papillae, which points towards the renal hilum [13]. The renal columns are branches of the connective tissue [15]. Parenchyma is formed by the renal cortex and the renal pyramids of the renal medulla. Within the parenchyma, there are approximately 1 million microscopic structures called nephron, which are functional units of the kidney [13]. The papillae are bundles of ducts that transport the urine produced by nephron to the calyces for excretion [15].

Microscopic Structure:
The kidney comprises between 1-2 million functional units, the nephron and a much smaller number of collecting ducts [11]. Nephrons are functional units of the kidneys where blood is filtered and urine is formed [15]. Every nephron consists of two parts: the renal corpuscle, where blood is filtered and the renal tubules through which the filtered liquid passes [13]. The afferent arteries form a tuft of high-pressure capillaries known as the glomerulus [15] and the glomerular (Bowman's) capsule, a double-walled epithelial cup that surrounds the glomerular capillaries that together form the renal corpuscle [13]. Continuing from the glomerular corpuscle, the remainder of the nephron is about 3 cm long and is described in three parts:

- The proximal convoluted tubule
- The medullary loop (Loop of Henle)
- The distal convoluted tubule [11]

The distal convoluted tubules of several nephrons are emptied into a single collection duct. Collecting ducts then merge and converge into several large papillary ducts, which drain into small calyces [13].

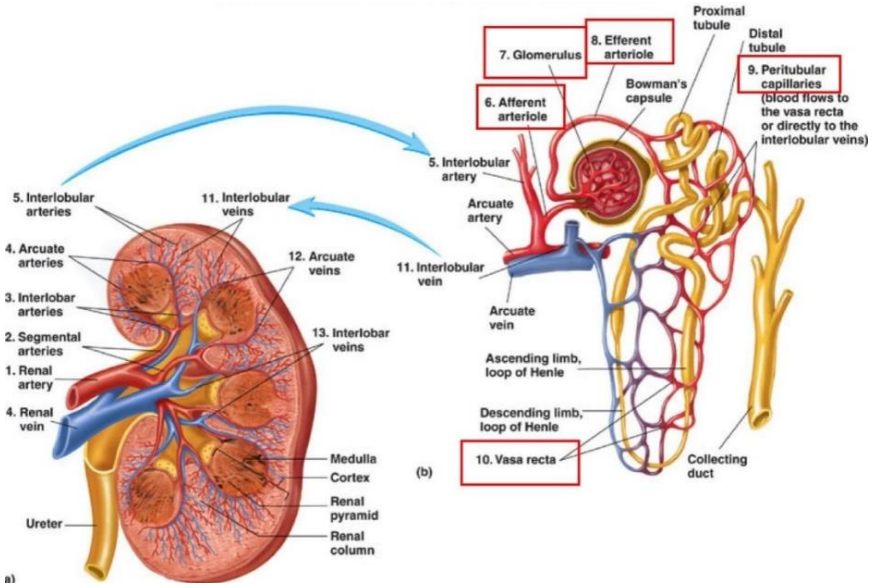

Figure 4: (a) Microscopic Structure of kidney; (b) Microscopic Structure of nephron [16]

Functions:

- Regulation of blood ionic composition
- Regulation of blood pH
- Regulation of blood volume
- Regulation of blood pressure by secreting enzyme renin
- Maintenance of blood osmolarity
- Production of hormones: calcitrol and erythropoietin
- Regulation of blood glucose level
- Excretion of waste and foreign substances

Ureters:
The ureters measure 25-30 cm long and are thick walled, narrow tubes ranging in length from 1 mm to 10 mm along the path between the renal pelvis and the urinary bladder [13].

Function:
Peristaltic contractions occur several times per minute, increasing the frequency with the volume of urine

produced, and moving small amounts of urine along the ureter to the bladder [11].

Urinary bladder:
The urinary bladder is a hollow distensible muscular organ in the pelvic activity posterior to the pubic symphysis [13]. The bladder is roughly pear-shaped, but it becomes more balloon-shaped as it fills with urine [11].

Function:
The urinary bladder is a reservoir of urine [11]. Its capacity is 700-800 ml on an average [13].

Urethra:
The urethra is a canal that stretches from the neck of the bladder to the outside of the urethral orifice [11].

Function:
In both males and females, the urethra is the terminal component of the urinary system and the process through which urine is discharged from the body. For males, semen is also discharged [13].

Types of Kidney Stones:
Based on variations in mineral composition and pathogenesis, the kidney stones are categorized as follows into five types:
1. Calcium stones
2. Uric acid stones
3. Struvite stones
4. Cystine stones
5. Drug-induced stones [9]

Stones differ in size, shape and chemical composition as depicted in the figure below [2].

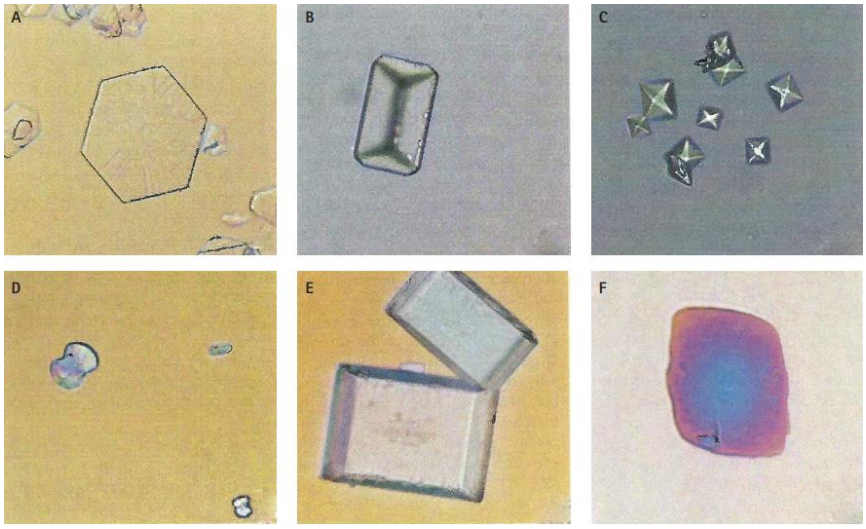

Figure 5: Types of stones. Light microscopy of urine crystals. (A) Hexagonal cysteine crystal (200X); (B) Coffin-lid shaped struvite crystals (200X); (C) Pyramid-shaped calcium oxalate dehydrate crystals (200X); (D) Dumbbell-shaped calcium oxalate monohydrate crystal (400X); (E) Rectangular uric acid crystals (400X); and (F) Rhomboidal uric acid crystals (400X) [2].

Approximately, 75% of urinary calculi are calcium based, 80% of which are calcium oxalate and 20% are calcium phosphate [8]. Of the rest, 10% are uric acid stones, 10% are struvite stones and less than 1% are cystine or are diagnosed as drug-induced stones [2].

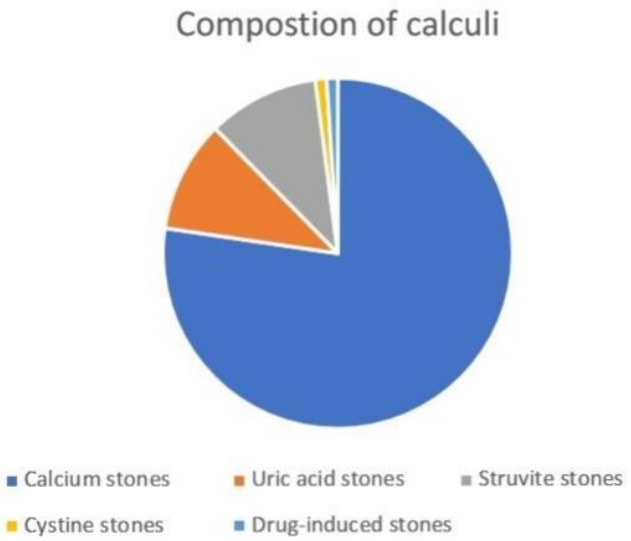

Figure 6: Composition of Calculi [2,8]

Calcium Stones:

Most calcium stones consist of calcium oxalate, either alone or more often in conjunction with calcium phosphate or calcium urate [2]. Calcium calculus pathophysiology is complex and involves low urine volume, hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia, and urinary pH abnormalities that lead to urinary supersaturation, crystal formation, and eventual aggregation into urinary calculus [7]. Urinary pH of 5.0-6.5 encourages calcium oxalate stones, while calcium phosphate stones occur when pH is greater than 7.5 [9]. Once a person forms a calcium-containing rock, another stone will usually form within less than 7 years, with the time period declining for subsequent stone events [7].

Uric Acid Stones:

These stones tend to form in individuals with hyperuricosuria. Urinary uric acid is produced from endogenous sources that are dependent on the dietary intake of proteins. Animal protein increases urinary calcium and uric acid, reduces urinary citrate and pH and improves bone resorption [17]. Uric acid is poorly soluble at a urinary pH of less than 5.5, but solubility improves at a pH greater than 6.5 [8]. Diets high in purines, particularly those containing animal protein diets such as meat and fish, result in hyperuricosuria, low urine volume and low urinary pH (pH<5.05) intensify the formation of uric acid stone [9]. Some patients with gout have mild uric acid overproduction, while others with genetic purine utilization defects, such as Lesch-Nyhan syndrome, have substantial uric acid overproduction. Patients with myeloproliferative disorders often over-produce uric acid and may have massive uric acid release during effective treatment, the so-called "tumor lysis syndrome" [7]. Approximately 15-20% of patients with clinical gout have uric acid nephrolithiasis [2]. Uric acid stones are more common in men than women [9]. Hydration, dietary purine restriction, urinary alkalization and, if needed, allopurinol administration are the core concepts of treatment for uric acid urolithiasis [7].

Struvite Stones:

Struvite stones are also known as triple phosphate stones or infection stones [7]. Struvite stones are caused by urinary tract infection with urease formed by organisms such as Pseudomonas, Klebsiella, Proteus, Staphylococcus and Escherichia coli [17]. Urease is required to split/cleave urea into ammonia and carbon dioxide, making the urine more alkaline, which increases pH [9]. Struvite stone formation happens only when the production of ammonia decreases and the pH of the urine increases, which reduces the solubility of phosphate [2] yielding to a large staghorn stone formation [9]. Infection is difficult to control since regular urine flow, which can wash off bacteria, is interrupted. Hematuria is normal and renal insufficiency and failure can occur due to obstruction and infection [7]. There is no role of dietary therapy in the management of struvite stones [17]. Percutaneous nephrolithotomy is often used to completely remove struvite stones [7]. They also grow back after surgical removal due to any residual infected fragments of stone [2]. Women are more likely to develop this type of stone than men, probably because urinary tract infections are more common in women [9].

Cystine Stones:

Cystine stones are the result of cystinuria, an autosomal recessive disorder that causes chromosome

2 defect in the rBAT gene, resulting in impaired renal tubular reabsorption of dibasic amino acids [17] which results in increased urinary excretion of cystine, ornithine, lysine and arginine [7]. Cystinuria occurs similarly in both males and females, while males are more severely affected [2]. Nephrolithiasis usually presents by the fourth decade and it is the only clinical manifestation [7]. The stones tend to be large, numerous and bilateral. The diagnosis can be made by finding standard hexagonal crystals in the urine. Urinary tract infection and obstruction is normal, as is stone recurrence every 1-4 years [2].

Drug-Induced Stones:

Drugs such as guaifenesin, triamterene, atazanavir, sulfa drugs and protease inhibitor, indinavir sulphate induce these stones [8]. These lithogenic drugs or their metabolites may be deposited in the form of nidus or in renal calculi that are already present. On the other hand, such drugs can cause the formation of calculi through their metabolic action through interaction with calcium oxalate or purine metabolism [9].

Pathophysiology:

Figure 7: Diagrammatic representation of the main steps in the formation of stone [18]

The pathophysiology of kidney
stone formation is complex and includes a combinatio n of metabolic, genetic and environmental factors [8]. Kidney stones occurs due to the supersaturation of urine by stone forming elements, including calcium, oxalate and uric acid. Supersaturated solution refers to a solution that contains more soluble content than could usually be dissolved by a solvent [9]. Crystals or foreign bodies that act as nidi on which supersaturated urine ions form microscopic crystalline structures. The resulting calculi give rise to symptoms when they are impacted within the ureter as they pass towards the urinary bladder [19]. The sequence of events that triggers the formation of stones can be classified into four stages which are as follows: [20]

- STAGE I: Crystal Nucleation
- STAGE II: Crystal Growth
- STAGE III: Crystal Aggregation
- STAGE IV: Crystal Retention

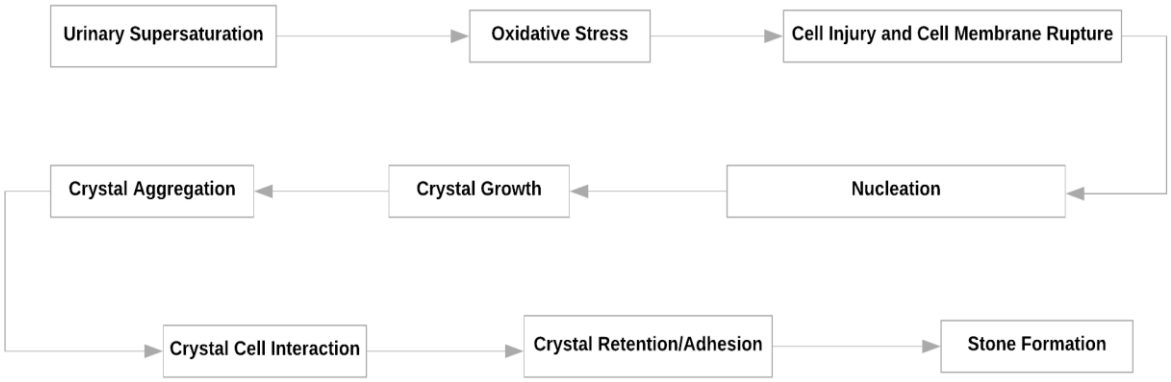

Figure 8: Schematic representation of the various events of kidney stone formation [9]

STAGE I: Crystal Nucleation:
Nucleation is the mechanism by which free ions in solution associate into microscopic particles [21]. The first step in the formation of kidney stone starts with the formation of a nucleus of supersaturated urine retained inside the kidneys. In a supersaturated liquid, free atoms, ions, or molecules, begins to form microscopic clusters, which precipitates when the bulk free energy of the cluster is less than that of the liquid [9]. For example, Ions such as calcium, oxalate, which have been filtered into the urine by the kidneys, spontaneously join together to form a solid crystal nidus [20]. Once a nucleus is formed, crystallization may occur at a lower chemical pressure than is needed for the formation of initial nucleus [9]. Nucleation is further classified into two types:

1. Homogenous Nucleation
2. Heterogenous Nucleation

Homogenous Nucleation:
It is defined as the formation of crystals around the nucleus with the same composition.

Heterogenous Nucleation:
It is defined as the deposition of organic materials like cell debris as a layer between the crystals [20].

STAGE II: Crystal Growth:
The tiny crystal formations travel down the nephron and are deposited at the renal papilla [20]. Urinary crystals stick together to form a small hard m ass of stone called crystal growth [9]. The growth of microscopic crystals is accomplished b y the movement of ions out of solution to the growing crystal [21] or secondary crystal nucleation on the matrix-coated layer. The process of stone growth is slow and takes longer time to block the renal tubules [9].

STAGE III: Crystal Aggregation:
Aggregation is a process of agglomeration of crystals that form into larger multi-component particles in a free solution [21]. Aleign T et al defined crystal aggregation as the process whereby a small hard mass of a crystal in solution sticks together to form a larger stone. It is considered to be the most critical step in the formation of the stone [9] and crystals can aggregate very quickly [20].

STAGE IV: Crystal Retention:
The binding of grown crystals to the renal tubule of the epithelial cells is referred to as crystal retention [9]. New stones are retained in the kidneys where they can continue to grow until they are moved and pass through the kidneys to the ureter [20]. This result in the movement of crystals from basolateral side of cells to the basement membrane where crystals could be added to the cells [9].

Risk Factors:
Risk factors do not have a direct cause of the disease, but in some way or another they are associated with it. Most literature and studies show that there is no exact cause of urinary calculus, but there are a variety of hereditary body reactions to certain metabolic and chemical factors and life-style threats that lead to the development of renal calculi [1]. Patients with a family history of nephrolithiasis have a 2.5 times higher risk of stone formation [2].

S. No	RISK FACTORS
1.	**Lifestyle Habits & Dietary Factors** Excessive intake of animal protein Excessive intake of salt Deficiencies of Chelating Agents (Citrate, Fibre, alkali foods) Sodium Oxalate Vitamins (C, D) Low Calcium Diet Potassium & Citrate
2.	**Metabolic Disorders** Hypercalciuria Hypocitraturia Hyperoxaluria Hyperuricosuria Gout Obesity
3.	**Hypercalcemia Disorders** Hyperparathyroidism
4.	**Urine composition** Excessive excretion of promoters of urinary crystallization Calcium (Idiopathic Hypercalciuria) Oxalate (Enteric Hyperoxaluria) Uric Acid (Uric acid hyperexcretion) Reduced excretion of inhibitors of urinary crystallization Hypocitraturia Hypomagnesemia
5.	**Low Urine Volume** Inadequate water intake Dehydration
6.	**Recurrent Urinary Tract Infections** Abnormalities of Urinary pH dRTA Gout Infection Stones Alkalinization of urine by bacterial urease *(Proteus mirabilis)*
7.	**Genetic Disorders** Family history of stones Genetic monogenic diseases Renal tubular acidosis Hyperoxaluria Cystinuria Dent's Disease Hypomagnesemia Hypercalciuria Nephrocalcinosis Bartter Syndrome (Type III & IV)
8.	**Anatomical abnormalities** Medullary Sponge Kidney Ureteropelvic junction stenosis Pyeloureteral duplication

	Polycystic renal disease Horseshoe kidney Solitary kidney
9.	**Hypertension, Diabetes Mellitus & Obesity**
10.	**Climate** Heat Water Loss Sweating
11.	**Systemic Diseases** Gastrointestinal Inflammatory Bowel Disease
12.	**Absence of Oxalate degrading bacteria**
13.	**Lithogenic Drugs** Indinavir Triamterene Sulfadiazine Uricosuric Agents

Table 1: Risk factors associated with Nephrolithiasis [2, 9, 24]

Clinical Manifestations [1, 22]

- Abdominal Pain
- Back Pain
- Problem in voiding urine
- Urinary Urgency
- Burning Sensation in urine
- Dark coloured urine
- Nausea and vomiting
- Hematuria

Diagnosis [23]

- Ultrasound
- Computed Tomography (CT) Scan
- KUB-X Ray
- Intravenous Pyleography (IVP)

Treatment

Management of nephrolithiasis needs to be individualized. Clinical presentation, proper history, and laboratory tests help to determine whether urgent surgical or medical treatment is needed [24].

Non-Pharmacological Treatment [17, 24]

1. **Hydration**
   For low fluid intake, urine output is reduced and urine flow is slower, both of which increase the risk of stone formation. Current guidelines recommend drinking enough fluids to produce at least 2.5 L of urine daily. The only fluids that should be avoided are tomato, grapefruit, and cranberry juice, because tomato juice is high in sodium whereas grapefruit and cranberry juices are rich in oxalate.
2. **Citric Acid**
   Consuming fruit juice prevents the development of stone not only because it increases thevolume of urine, but also because it is high in potassium and citric acid. Citrate prevents the formation of stone by two mechanisms. First, it binds to urinary calcium, which reduces the supersaturation of urine. It also binds calcium oxalate crystals and prevents crystal growth.
3. **Calcium**
   There is a common misconception that a reduction in calcium intake will reduce the risk of calcium stone formation. Research have shown that low dietary calcium potentially increases the risk of developing symptomatic kidney stones. With low calcium intake, there is insufficient calcium in the digestive tract to bind to oxalate, leading to increased absorption of oxalate and excretion of urinary oxalate. The optimal calcium intake is 1,200 mg, equivalent to four 8-oz glasses of milk.
4. **Oxalate**
   Higher intake of oxalate has been shown to increase urinary oxalate levels. The best way to minimize the intake of oxalate is to control the consumption of these foods. Chocolate is a major source of dietary oxalate in younger women and should be used sparingly. Examples of high oxalate containing foods includes spinach, tomato, sweet potato, nuts etc
5. **Vitamins**
   Vitamin C, contained in supplements raises the level of urine oxalate since ascorbic acid is metabolized to oxalate. Vitamin B-6 (pyridoxine), on the other hand, can reduce urinary oxalate.

Pharmacological Treatment:

1. **Potassium Citrate**
   Potassium citrate treatment causes a significant increase in urinary citrate, pH and potassium, resulting in significantly less stone development [17]. Potassium Citrate therapy appears to increase urinary citrate mainly by modifying the renal handling of citrate rather than by increasing the filtered load of citrate. Potassium citrate causes changes in urine, rendering the urine less resistant to the development of crystals and salt stones. Higher citrate levels in the urine can induce calcium complexion which decreases calcium ion activity and reduces the chance of calcium phosphate crystal formation [26].
2. **Thiazide Diuretics**
   Thiazide diuretics minimize sodium reabsorption by inhibiting the NaCl cotransporter in the distal convoluted tubule and by increasing calcium reabsorption [17, 29]. It promotes sodium [27] and water loss from the body. Thiazides also inhibit the transfer of sodium ion through the renal tubular epithelium by binding to a thiazide-sensitive sodium chloride transporter. It results in an increase in potassium excretion through the sodium-potassium exchange system [28].
3. **Allopurinol**
   Allopurinol is a structural analogue of the natural purine base, hypoxanthine [30]. It was synthesized as a purine antimetabolite for cancer chemotherapy. However, this did not have antineoplastic activity but was an inhibitor of xanthine oxidase [31]. Allopurinol inhibits the production of uric acid by acting as a competitive inhibitor of xanthine oxidase, an enzyme which transforms xanthine to uric acid [17]. It lowers uric acid levels in a dose dependent manner [32]. The effect is a fall in the plasma urate level and a decline in the total urate burden [33] resulting in decreased uric acid concentrations in the serum and urine [30].
4. **Antibiotics [34]**
   Certain antibiotics are given in order to prevent infections and for the management of severe complications caused due to nephrolithiasis. These medications (Ampicillin, Gentamycin, Fluoroquinolones such as Ciprofloxacin, Levofloxacin, Ofloxacin [34], Acetohydroxamic acid [25]) are those used in the emergency department and in the outpatient treatment [35]. In addition to these, drugs from other class of antibiotics may also be used.

a. Ampicillin
Ampicillin is a beta-lactam penicillin antibiotic used in the treatment of bacterial infections. It is chemically known as D-alpha-amino benzyl penicillin [36]. The bactericidal activity of Ampicillin results by its binding to specific penicillin-binding proteins (PBPs) within the bacterial cell wall, Ampicillin inhibits the third and final stage of bacterial cell wall synthesis. Cell lysis is then mediated by the bacterial cell wall [37].

b. Gentamicin
Gentamicin is a broad-spectrum aminoglycoside antibiotic obtained from *Micromonospora purpurea* [39, 40]. It functions by binding to the bacterial 30S ribosomal subunit, causing misreading of t-RNA, leaving the bacterium unable to synthesize proteins that are essential to its growth [38].

c. Fluoroquinolones
They act by inhibiting topoisomerases of type II bacteria, topoisomerases of type IV, and DNA gyrases. It inhibits the A subunits of DNA gyrase, two subunits encoded by the gyra gene. It results in strand breakage, supercoiling, and resealing of the bacterial chromosome; DNA replication and transcription are inhibited [41]. Some of the fluoroquinolones includes Ciprofloxacin, Levofloxacin, Ofloxacin.

d. Acetohydroxamic acid
Acetohydroxamic Acid, a synthetic product derived from hydroxylamine and ethyl acetate, is similar in structure to urea. It acts by the reversible inhibition of the bacterial enzyme urease. It prevents the hydrolysis of urea and the production of ammonia in urine infected with urea-splitting bacteria, leading to a decrease in pH and ammonia levels [42].

5. **Tiopronin**
   Tiopronin is recommended for the prevention of kidney stone development in patients with severe homozygous cystinuria with a urinary cystine level greater than 500 mg/day. Kidney stones form when the solubility limit is reached and the urine is supersaturated with endogenous cystine. Tiopronin is an active reducing agent that undergoes a thiol-disulfide exchange with cystine to form a water-soluble mixed disulfide complex. Through reducing urinary cystine concentrations below the solubility point, tiopronin helps to reduce the development of cystine stones [43].
6. **Tamsulosin**
   Tamsulosin is effective in expulsion therapy as it increases the passage rate and reduces the passage

time for stones up to 10mm [24]. Tamsulosin is an alpha adrenoceptor blocker with specificity for the alpha-1A and alpha-1D subtypes. Through blocking these adrenoceptors, the smooth muscle of the prostate is relaxed and the urinary flow is improved. Blocking alpha-1D adrenoceptors relaxes the detrusor muscles of the bladder, which avoids storage symptoms.

TYPE OF KIDNEY STONE	MEDICATION
CALCIUM STONES	Potassium Citrate Diuretics
URIC ACID STONES	Allopurinol Potassium Citrate
STRUVITE STONES	Antibiotics Acetohydroxamic Acid
CYSTINE STONES	Tiopronin Potassium Citrate

Table 2: Recommended drugs for different types of Stones [25]

Surgical Treatment:

1. **Extracorporeal Shockwave Lithotripsy**

Extracorporeal shock wave lithotripsy (ESWL) is a non-surgical procedure which uses shock waves to break stones into small pieces [2]. After the treatment, the kidney stones should be tiny enough to move out of your body in your urine [45]. A stone is fragmented when the force of a shock wave overcomes the tensile strength of a stone. When a shock wave travels through a medium (water), it loses very little energy until it passes into a medium with a different density. If the medium is denser, the compressive forces are produced on the new medium. Similarly, if the new medium is less dense, the tensile stress on the first medium is produced. Upon hitting the anterior surface of a stone, the change in density creates compressive forces, causing fragmentation. As the wave proceeds through the stone to the rear surface, the shift from high to low density reflects part of the energy of the shockwave, producing tensile forces that again disrupts and fragments the stone [46].

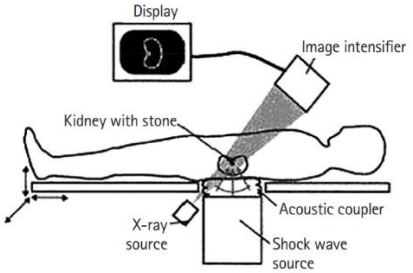

Figure 9: Representation of Extracorporeal shock wave lithotripsy (ESWL) [2]

2. **Ureteroscopy**

It is a technique in which a small scope (Ureteroscope) [22] is inserted into the ureter [47] and used to detect stones in the ureter [48]. Rigid telescopes are used for stones in the lower part of the ureter or the bladder. Flexible telescopes are used to treat stones in the upper ureter and kidneys [22]. Once the stone has been identified a special tiny laser fibre is used to break the stone into very fine fragments, which are then left to pass naturally, or if big enough, then removed with tiny baskets put through the frame [36]. This is an outpatient procedure with or without inserting a stent [47]. At the end of the procedure, most surgeons leave the stent which is a tiny rigid plastic tube that helps keep the ureter open so that the urine can flow from the kidney to the bladder [22]. The stent is placed because the ureter is swollen after the instrumentation and the swelling can block the kidney after surgery [49].

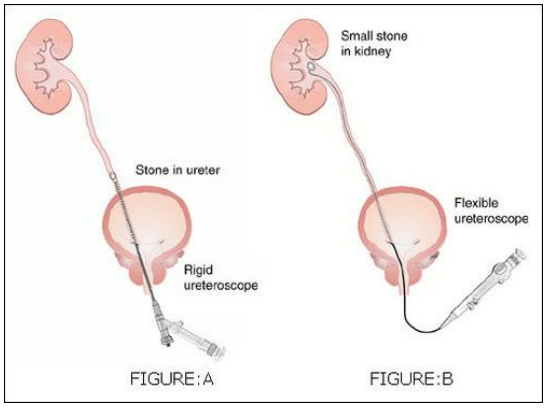

Figure 10: Types of Ureteroscope [50]

3. Percutaneous Nephrolithotomy

Percutaneous nephrolithotomy is a technique used to extract kidney stones from the body when they cannot exit on their own. A scope is inserted through a small incision in your back [51] just large enough to allow a rigid telescope (nephroscope) to pass through the hollow centre of the kidney where the stone is located [22]. This approach helps to reach the kidney directly from the skin without passing through the bladder or ureter [52]. An instrument passed through the nephroscope splits the stone and suctions the pieces the ability to suction the fragments makes PCNL the best treatment option for large stones. Normally, after PCNL, a tube is left in the kidney to drain urine into a bag outside the body This will also help to stop any bleeding [22].

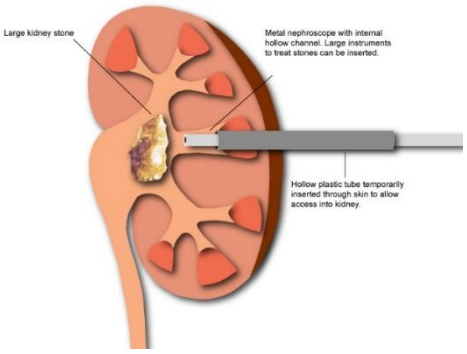

Figure 11: Percutaneous Nephrolithotomy [53]

CONCLUSION:

Kidney stones are common and recur frequently. Many aspects of renal stone formation remain unclear. Nevertheless, it is certain that renal cell damage, crystal retention, cell apoptosis and associated stone inhibitors or promoters play an important role in the formation of kidney stones. Calcium oxalate stones are the most common ones. The dietary factor is very significant among the different risk factors for stone formation. Citrate is the most common crystal formation inhibitor and urinary pH is very important for the prevention and treatment of different types of stones. Stones that are painful or too large to pass spontaneously and stuck in the urinary tract need to be removed by surgery. By incorporating nutritional and medical treatment for stone prevention, the risk of stone recurrence can be significantly reduced and the quality of life improved. Therefore, recognizing the underlying pathophysiology, risk factors and genetic basis of kidney stone formation will potentially lead to the discovery of medications and nephrolithiasis management strategies for the future.

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