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Study on Renal stones: A review

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ABSTRACT:
Renal stones represent one of the most prevalent urological conditions, arising from the abnormal accumulation of crystalline materials within the kidney, ultimately leading to renal impairment and urinary tract obstruction. This affliction encompasses four distinct types categorized by their chemical composition, with analysis typically conducted through Fourier Transform Infrared Spectroscopy. Numerous studies have highlighted the significant prevalence of bacterial presence in renal stones, correlating with a heightened risk of urinary tract infections among urolithiasis patients. This study provides a comprehensive overview of renal stones, exploring their various types, morphologies, diagnostic methodologies, risk factors, pathogenesis, and clinical manifestations, while also delving into the associated infection dynamics. The bacterial species isolated from stone samples are thoroughly examined, elucidating their bacteriological profiles, with particular emphasis placed on their interactions with different stone types.

1. Introduction

Renal stones also called nephrolithiasis and urolithiasis a frequently encountered urological disorder in which mineral stones develops in the urinary tract which includes kidneys, ureters, bladder, and urethra[1]. Kidneys are responsible for excreting minerals and other substances from the blood samples but due to various etiological reasons these substances stick together to make crystals and these crystals bind together and form stones[2]. The prevention of renal stone recurrence is still a significant issue in human health problem. The overall prevalence of renal stones is increasing worldwide where 10% of all individuals will develop renal stones in their lifetime and it is more common in men compared to women worldwide. Among all countries, North America has the highest prevalence of renal stone disease, about 7 to 13%, Europe 5 to 9%, and Asia 1 to 5%[3]. In India, the prevalence rate is high in northern India compared to southern India[4]. There are 30% to 40% risk of developing stones for the second time in those patients who developed renal stone disease for the first time if they do not apply metaphylaxis. The estimated rate of recurrence in one year is about 10%, in five years it is estimated as 35% and it is 50% in ten years[5]. Stone samples are made up of different types of chemical compositions, and based on that stones are differentiated as calcium stone, struvite stone, uric acid stone, cystine stone, and drug-induced stones[5]. Among all the types, calcium stones are the most frequently isolated renal stones which is reported about 80%. The second frequently isolated stones are uric acid stones, and it is found to be 10% to 15%. Struvite stones are found to be 3% to 10% followed by cystine stone types which are estimated as less than 2%. The least frequent isolated stones are drug-induced stones which are reported as less than 1%. The symptoms of renal stones depend on their location in the urinary tract. The formation of stones does not cause any symptoms in the early stage. But when it grows big enough, it causes symptoms like renal colic, flank pain, hematuria, and

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

blockage of urine flow, hydronephrosis, and urinary tract infection where these conditions lead to nausea and vomiting[6]. Renal stones are diagnosed by different methods which include blood tests, urine tests, and imaging techniques like CT scans, abdominal X-rays, and ultrasound techniques. Microbiome which includes urea-producing bacteria, nanobacteria, and intestinal microbiota plays a crucial role in forming renal stones[9]. These bacterial infections lead to form stones by promoting crystal adhesion which causes tissue inflammation, synthesis of organic matrix, and crystal matrix interaction[7]. Struvite stones are considered to be the infective type that was formed by many urea-producing bacteria, the *proteus species* are the most common bacteria to form these infective stones in all ranges of age[10]. Nanobacteria appear to contribute too many calcifying diseases including renal stone which represents a common problem with inadequate prevention. These nanobacteria can be detected by different methods which include nanobacteria-specific monoclonal antibody, ELISA, and culture methods[11].

2. Methods

This review was conducted across multiple scientific databases, including PubMed, Scopus, and Google Scholar, utilizing keywords such as "renal stones," "urolithiasis," "risk factors," and "diagnosis." Research studies published between 1939 and 2023 were included in this comprehensive review.

3. Types of renal stones:

Renal stones are differentiated into five types based on their size, shape, and chemical composition (Fig 1). The estimated volume and diameter of stones isolated from the male are smaller compared to the female.

3.1. Calcium stones:

Calcium stones were first discovered in the second half of the 18th century[12]. These stones are the more frequently isolated type in renal stone disease which is differentiated into two types based on their chemical composition (e.g. calcium oxalate monohydrate CaOx and calcium phosphate dihydrate CaP). The prevalence rate of the calcium oxalate type is high compared to the calcium phosphate type, sometimes both types were also detected with the same sample. The estimated size of calcium oxalate monohydrate has the lowest diameter of stone and its volume (3.6mm and 9.0mm^3) compared to other types[13]. These calcium stones have the highest recurrence rate compared to all other types[14].

3.2. Uric acid stones:

Uric acid stones were first discovered in 1776[15.] These stones have the chemical composition of ammonium urate and ammonium phosphate[17]. This is the second most frequent type of stones in renal disease[18]. These stones have a diameter of 7mm. Acidic urinary pH plays an important factor in forming this type of stones[19].

3.3. Struvite stone:

Struvite stones were first discovered in 1845. This type of stone has the chemical components of magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4.6H_2O$). Struvite stone has the highest diameter and volume of stones among other types (7.9mm and 61.0mm^3) [13]. These stones are formed due to urea-producing bacteria colonizing in urinary tract. It can grow into a larger size rapidly if not treated, which leads to cause 50% chance of losing one kidney. The recurrence rate of this type of stone is higher in females compared to males[15].

3.4. Cystine stones:

Cystine stones were first discovered in 1833. These stones are the second least frequent types which is estimated at 1% to 2% and also it is estimated as 6% to 8% in paediatric calculi. This type of stone is formed in patients with a genetic disorder known to be cystinuria, where 80% of these patients will develop their first stone in the first two decades of life. Mostly, cystinuria patients will develop pure cystine stones but they are also developing mixed stones which contain calcium oxalate, phosphate, or struvite. Cystine stone formers will develop larger size of stones compared to calcium stone formers[20].

3.5. Drug-induced stones:

Drug-induced stones are first reported in 1940[21]. This is the least frequent type of stone among others. These stones are divided into two different groups the first group includes the drugs that are poorly soluble with high urine excretion and this condition leads to form crystallization in the urine. The second group includes the drugs that induce stone formation by interfering

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with the metabolism of calcium, oxalate, phosphate, uric acid, or other purines[22].

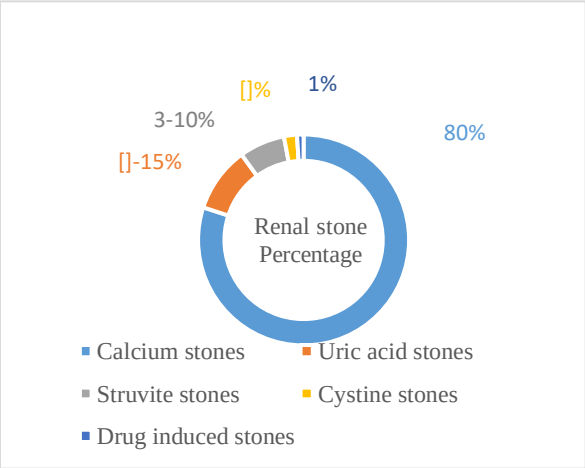

Fig: 1 Pictorial representation of different types of renal stones present in urolithiasis patients.

4. Morphology of stone types[23]:

The morphology of stones is studied by the classification of Michel Daudon's morpho-constitutional analysis[23]. Morphological examination of the outer surface is analyzed by stereomicroscope which can provide a three-dimensional view of stones and the inner surface is analyzed by Fourier-transform infrared spectroscopy (FTIR) which can provide its chemical compositions[24,25]. By following Michel Daudon's morpho-constitutional analysis, stones are differentiated into 6 types (I – VI). These types are further divided into different subtypes based on their corresponding conditions.

4.1.1 Calcium stones:

Calcium stones are further classified into two types. Type 1 stones are mainly composting calcium oxalate monohydrate (COM) which is subdivided into six morphological subtypes. Type 2 stones are composed of calcium oxalate dihydrate (COD) which has three different morphological subtypes.

4.1.2. Calcium oxalate monohydrate (COM)

Type 1a:

Type 1a is the most frequently isolating idiopathic calcium stone type. Morphology of this type is described as round in shape, smooth, and dark brown surface. In some conditions, greyish thin superficial deposits may be seen on this type of stone surface this can be considered as metabolically inactive form[25,26].

Type 1b:

This is the second frequently isolating type. In this type, the morphology of the stone is described as dark-brown color, rough surface with unorganized sections, and without umbilication[26,27].

Type 1c:

Type 1C is the least frequently isolating type of stone where it acts as a pathognomonic for primary hyperoxaluria type 1 and type 2. The type 1C stone morphology is characterized as a yellowish budding surface, pale in color with unorganized section[28].

Type 1d:

This type of stone leads to the form of urine status where it will get smoothen by contact with other stones. Morphological characterization of this type is described as a beige or pale brown smooth surface and its concentric layers are made without radial organization.

Type 1e:

The structure of this type of stone is described as intermediate between type 1a and type 1c where it corresponds to fluctuating excretion of oxalate in urine. This type of stone is showing budding with clumsy pale brown-yellow areas where it gets mixed with dark brown layers[27]. All the types are illustrated in Figure 2.

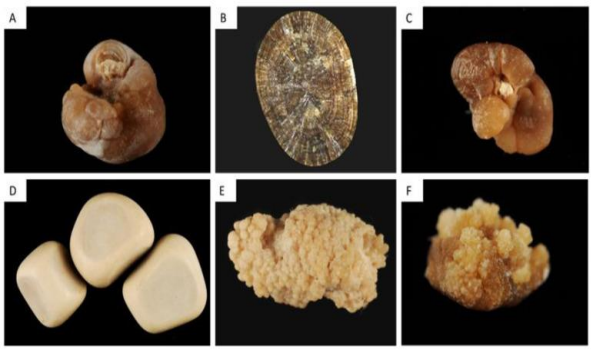

Fig: 2 Types of Calcium oxalate monohydrate stones (COM)

(A) Type 1a stones appear grey due to their recent deposition of crystalline on their surface. **(B)** Type 1a

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stones showing radial organization. **(C)** Type 1a stones in Randall's plague remnant. **(D)** Type 1d stones show smooth surfaces. **(E)** Type 1c stone with a typical whitish surface. **(F)** Type 1e stone formed due to enteric hyperoxaluria.

4.2. Calcium oxalate dihydrate (COD)

Type 2a:

This subtype of COD is considered to be most common among others. The morphology of these stones is described as a little brown and has sharp crystals on their surface[29].

Type 2b:

This subtype is estimated to be the second most frequently isolating COD. This surface color is described as little brown and has eroded crystals.

Type 2c:

The estimated amount of these subtypes is much less compared to others. The condition of hypercalciuria and storage of multiple stones in the same area leads to the form of this subtype of COD. This morphological study shows a pale brown surface[27].

4.1.3. Calcium oxalate trihydrate: (COT)

These stones are considered to be the rarest type in renal disease. Due to its hexagonal structure, their morphology is very difficult to characterize[26].

4.1.4. Mixed stones COM and COD:

COD stones may convert into COM type due to its more stability. This condition is more common in patients with hypercalcinuria and intermediate hyperoxaluria. This type of stone may be seen in Randall's plaque. The composition of this type of stone will be analyzed with the FTIR process[29]. These stones are shown in Figure 3.

Fig: 3 Types of Calcium oxalate dihydrate stones (COD)

(A) Type 2a stone with a unique sharp aspect. **(B)** Type 2a stone which shows poor organization. **(C)** Type 2b stone with less sharp crystallites than type 2a. **(D)** Type 2b stone with little brown and eroded crystals. **(E)** A mixture of type 1a and type 2b stone.

4.2. Uric acid stones:

Uric acid stones are further classified into three different types which are further described below

Type 3a:

These stones are formed with anhydrous uric acid. This surface appears smooth orange in color with concentric layers which it is more common in prostate hypertrophy-affected males.

Type 3b:

This type of stone is composed of pure uric acid in most of the isolated stones which are estimated at 77% where it is also seen with a mixture of other types of stones. This type of stone is more common in patients with ileostomy which leads to cause low urine excretion and pH[30].

Type 3c:

Increasing the pH of urine leads to form this type of stone and it contains the chemical compositions of urate salts, sodium urate, and the very least amount of potassium and calcium urate. They appear as grey or beige color on their surface[27].

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

Type 3d:

This type of uric acid stone was made up of ammonium hydrogen urate. It has a rough, porous surface and appears as dark-brown in color. This type is more frequently isolated from children who suffer from endemic bladder stones[31]. These type of stones are shown in Figure 4.

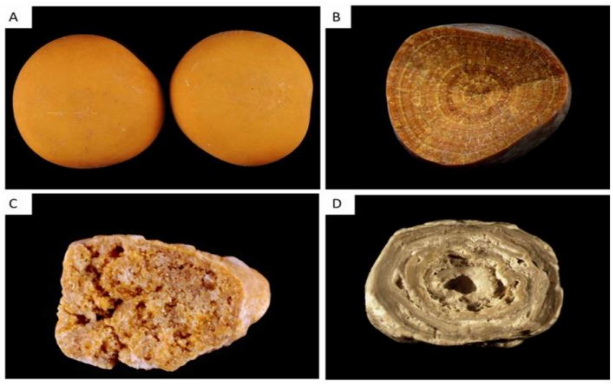

Fig: 4 Types of Uric acid stones

(A) Type 3a stone with smooth surface and orange color. **(B)** Type 3a stones with concentric layers. **(C)** Type 3b stone with porous structure. **(D)** type 3d stone showing an alternative thick layer and brown.

4.3. Struvite stones (Type IV)

These stones are made up of phosphate especially calcium phosphate (CaP) and magnesium ammonium phosphate in hexahydrate form. The suitable condition to form struvite stones was the high level of calcium and phosphate concentration in urine[26]. This type of stone was classified into 4 subtypes which are described below:

Type $4a_1$:

Most accurate calcium phosphate (CaP) stones come under this subtype which mainly contains carbapatite with the least amount of COM or COD. The morphology of these stones is described as white with poorly organized concentric layers.

Type $4a_2$:

The morphology of these stones is very peculiar, which is described as yellow-brown with glazy and cracked surfaces along with irregular yellow-brown concentric layers[32].

Type 4b:

This stone contains a higher composition of calcium apatite followed by other calcium phosphate, whitlockite, and struvite. These stones appear as dark brown, rough surfaces with whitish brown alternate layers.

Type 4c:

These stones are made up of struvite compositions with whitish surfaces. Its section is poorly organized with radial crystallization.

Type 4d:

These stones are made up of a unique form of calcium phosphate known as brushite. Its morphological structure was described as a whitish rough surface with typical radial organization of their section[27]. Figure 5 illustrates this type of stone.

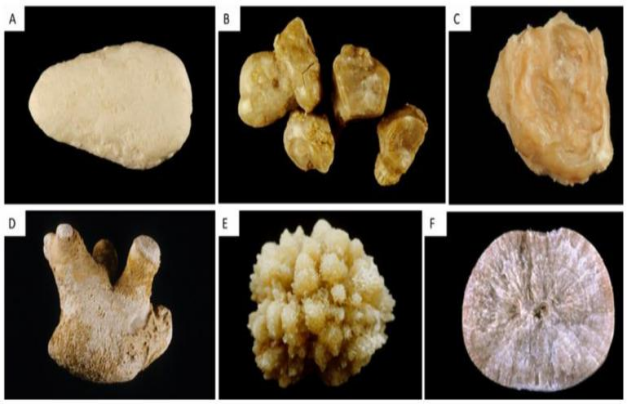

Fig: 5 Types of Struvite stones

(A) Type 4a1 stone with a smooth surface. **(B)** type 4a2 stone appears a yellow-brown color with cracks. **(C)** Type 4a2 stone showing irregular yellow-brown concentric layer. **(D)** Type 4b stone shows a heterogenous rough surface, and is clear to dark brown. **(E)** Type 4d stone shows a slightly rough cabbage-like surface and appears whitish to beige. **(F)** Type 4d stone shows radial crystallization with concentric layers.

4.4. Cystine stones (Type V):

These stones are composed of cystine which are formed due to the condition known as cystinuria. They are further differentiated into two subtypes based on their morphology. Subtype 1 appears as a yellowish color

Journal of Chemical Health Risks

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

with a rough surface whereas the other subtype appears as a creamy color with a smooth surface. These stones are shown in Figure 6.

4.5. Drug-induced stones (Type VI):

Usage of certain drugs may lead to the development of renal stones which are known to be drug-induced stones[33]. This type of stone is usually formed by high dose or long-lasting treatment of drugs and it can also be the result of low solubility of drugs, low urine excretion, and pH abnormalities in urine[34].

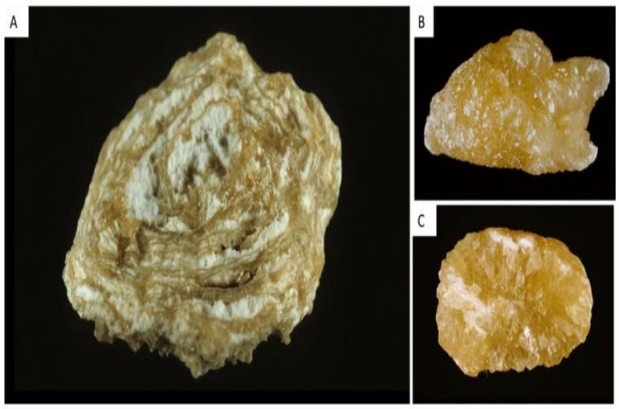

Fig: 6 Mixed and cystine stones

(**A)** The least amount of calcium phosphate is frequently isolated in type 11 stones in hypercalcinuria conditions. **(B)** Cystine stones appear yellow. **(C)** Cystine shone has rough and hexagonal crystalline on its surface.

5. Risk factors:

Globally, stone developers in males are higher compared to females, where it is found to be 12% in males and 6% in female[35]. The national health and nutrition examination survey reported that BMI, water intake level, dietary calcium intake, and sugar-containing beverages are estimated to be 50% of all renal stone diseases. Some studies have reported that renal stones are usually multifactorial where these patients have more than one risk factor and these conditions are described below[36].

5.1 Age and sex:

Renal stones can develop in any age even children, but higher incidence is estimated in males around 40-50 years whereas in females it is found to be 20-30 years [37]. The prevalence rate of renal stone disease is higher in males compared to females which is estimated at 2:1 but over the last decades, this prevalence has increased among female[38]. Pregnancy may also lead to form stone formation due to their elevated pH level in urine and increased urine calcium level. This condition is more suitable for developing calcium type of stones in mother[35]. This gender difference is not only applicable to prevalence and risk factors it is also indicating their stone types, where females have more prevalence of calcium phosphate and struvite type compared to male[39].

5.2 Obesity:

Obesity is defined as a person who has a BMI level of more than 20 kg/m^2 and is high at risk for developing renal stones, especially for calcium oxalate and uric acid stones[35,40]. Based on a 2019 global report, the prevalence rate of stone formers is increased in obese people which is found to be 6-8% in children, 3-11% in males, and 6-15% in female[41].

5.3 Genetics:

Development of renal stones is most common in people with a family history of renal stones when compared to other conditions this factor is estimated as a 50-60% risk for developing stones. The heredity risk is more common in males compared to female[42]. There are more than 40 genes have been discovered that can develop stone formation. In inheritance, there is a gene known as SLC34A1, which is more severe and difficult to diagnose after birth[43]. In children, monogenic stones are rare but they play a major part in renal disease.

5.4 Nutrition:

There are certain nutrition plays a crucial role in renal stone formation. Some nutrition is estimated lower level in renal patients and some are high level[44]. Those nutrition's are described below.

Calcium: A high level of calcium leads to a lower risk of stone formation by reduced oxalate absorption in the intestine[45].

Oxalate: Only a certain amount of oxalate is excreted by kidneys, which is observed from the intestinal oxalate

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

and the major part is derived from vitamin C, glycolate, and hydroxyproline[46].

Animal protein: Animal protein has a high level of phosphate which will provide a higher load of acid due to its sulfur-containing amino acid content, where this content will release sulfuric acid by metabolism conversion and it will be excreted by kidneys. Some studies have reported that less amount of meat intake leads to reduced risk for renal stone development[47].

Salt and potassium: A high level of salt intake leads to reduced renal reabsorption of calcium whereas a high level of potassium intake will reduce calcium excretion by increasing urinary salt excretion[48].

Citrate: Citrate is one of the major inhibitors for crystal formation where hypocitraturia condition is considered as a major risk factor[49].

5.5 Water:

Several studies have reported that increased amounts of water lead to reduce the primary and secondary causes of nephrolithiasis[47].

5.6 Dietary supplement:

In developed countries, dietary supplements are widely used. Overtaking supplements of vitamin C and vitamin D are more common in increasing the risk for stone formation[50].

5.7 Systemic disorders:

Certain systemic disorders lead to the development of renal stones which are known as diabetes, primary hyperthyroidism, metabolic syndrome, Crohn's disorder, and GOUT[37].

5.8 Microbiome:

Several studies reported that gut microbiome can lead to prevent the formation of oxalate stone[18]. Overuse of antibiotics may alter the gut microbiome which will lead to increased risk for stone development[52].

5.9 Climate:

Climate changes due to global warming lead to an increase in the risk of stone formation[53]. This high level of temperature can also be achieved by dehydration and blood hyperosmolality[52].

5.10 Urinary tract infections:

Certain studies have reported that urinary tract infections may lead to an increased risk for stone formation. Struvite stones are highly developed by this condition followed by calcium oxalate and calcium phosphate stones where it is most prevalent and estimated in high-age females[53].

5.11 Drugs:

Certain antibiotics can directly induce stone formation by increasing hyperoxaluria, causing dysbiosis or low solubility. Such antibiotics are sulphonamides, ceftriaxone, and trimoxazole[54].

6. Diagnosis:

For diagnosis of renal stones, systemic and environmental influence of patient information should be carefully investigated. There are many special methods available for diagnostic purposes which are described below.

6.1 Blood investigation:

This investigation will help to analyze the amount of serum sodium, potassium, bicarbonate, calcium, creatinine, and urate in blood samples and the normal values are showed in Table 1[55]. If we find any abnormalities in this analysis it will take further investigation.

Investigation	
Serum sodium	135-145 mEq/L
Potassium	3.5-5.0 mmol/L
Bicarbonate	23-29 mmol/L
Calcium	8.6-10.2 mg/dL
Creatinine	0.7-1.3 mg/dL (Men) & 0.6-1.05 mg/dL (women)
Urate	25-80 mg/L (Men) & 15-60 mg/L (women)

Table: 1 Normal values of the relevant analyst in Blood

6.2 Urine investigation:

The urine sample will be used for different investigations which include, their pH, calcium, uric acid, oxalate, sodium, potassium, citrate, and creatinine[55]. These normal values are mentioned in

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

Table 2. There are various methods are available for processing urine samples but at present, 24 hours of urine is the most recommended and accepted method for investigation[56].

Investigation	
Calcium	25-300 mg/ 24hrs (Men) & 20-275 mg/24hrs (Women)
Oxalate	45mg/24hrs
Magnesium	2.1-23.2 mg/dL (Men) & 0.6-13.7 mg/dL (Women)
Uric acid	2.5-7.0 mg/dL (Men) & 1.5-6.0 mg/dL (Women)
Cystine	15-140 µmol/24hrs (Men) & 15-55 µmol/24hrs (Women)
Citrate	0.04-0.33 mmol/ (Men) & 0.11-0.55 mmol/ (Women)

Table: 2 Normal values of the relevant analyst in Urine

6.3 Imaging techniques:

A highly sensitive technique for renal stone diagnosis is abdominal compound topography (CT) which is considered to be the golden standard technique[57]. Masuomy et al. in 2021 reported that the sensitivity of CT scans for renal stones is 86.27%[58]. This CT scan will provide more accurate, rapid information and a significant density of stones[59]. Rodger F et al., in 2018 conducted a test on "Diagnostic Accuracy of Low and Ultra-Low Dose CT for Identification of Urinary Tract Stones: A Systematic Review" and reported that low-dose CT scans correctly detected renal stones in 90% to 98% where 88% to 100% correctly found that if stones are not developed[60]. Abdominal X-ray is one of the imaging techniques for the initial diagnosis of larger stones, where stone fragility can be studied early. This technique can help to detect the size and location of renal stones in the urinary tract but it is not used as often as other techniques because it may not find smaller types of stones in the urinary tract[61]. Ultrasound (US) is one of the effective techniques for the diagnosis of symptomatic renal stones. However, this US is found to be less sensitive and less accurate in stone investigations compared to CT scan[62]. The sensitivity of this US is estimated to be 24% to 70% less compared to CT scan[63,64].

7. Pathogenesis:

Stone formation process is involved by changing their phase into supersaturation, where dissolved salts are constricted as solid[1]. Among the different types of calcium stones, the most common isolated type is calcium oxalate which is approximately 80% followed by calcium phosphate 15%[65]. The mechanism of this calcium type of stone is difficult and diverse which includes hypercalcinuria, hypocitraturia, hyperuricosuria, hyperoxaluria, and abnormal pH in urine[66]. The mechanism for uric acid stone formation includes low urine volume and unduly acidic urine and it also includes hyperuricosuria. Cystine stone mechanism takes place in renal tubular disorders and the infectious type of struvite stone mechanism is based on bacteria that can produce urea. All these conditions are described below.

7.1 Hypercalcinuria:

The relationship between hypercalcinuria and nephrolithiasis was first described by flocks in 1939[67]. The term idiopathic hypercalcinuria was first introduced by Albright and Henneman in 1952[68]. This condition is more common in patients who develop calcium stones, which is estimated about 30% to 60% in adult nephrolithiasis[69]. Mechanism of hypercalcinuria may involve, increasing calcium absorption in the intestine, decreasing reabsorption of renal calcium, increasing metabolism of calcium from bone, and hyperabsorption of calcium in intestine[70]. This condition is classified into two different variants, the severe variant is characterized by hypercalcinuria, hyperabsorption of calcium in the intestine, normocalcemia, and change in serum parathyroid hormone level, and the less severe variant also characterized by these same conditions except in hypercalcinuria, where this condition can be normalized by restricted diet in calcium which is identified as less than 400 mg/d[71].

7.2 Hypocitraturia:

This is one of the most common metabolic abnormalities in calcium stone formers, where it is found to be 20% to 60%[72]. During this condition, the excreted amount of citrate in urine is reduced to less than 300mg per day and it more commonly occurs with metabolic acidosis[73].

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

7.3 Hyperoxaluria:

Hyperoxaluria is a condition where a higher amount of oxalate is excreted in urine which is estimated at 10% to 50% in stone formers. This urinary oxalate and calcium are more responsible for calcium oxalate stone formation[74]. The mechanism of this condition includes the overproduction of oxalate, which leads to an inborn error of metabolism, absorption of intestinal oxalate, and increased food intake[75]. This condition is associated with certain factors that can increase the risk of stone formation including hypocitraturia, hypomagnesuria, decreased urine volume, and acidic urine[76].

7.4 Hyperuricosuria:

Hyperuricosuria is a condition where an excess amount of uric acid is excreted in urine. This is the least common metabolic abnormality seen in calcium stone formers, about 10% of calcium stone formers have developed this condition. But somehow this condition is occurring more in calcium stone formers with other metabolic abnormalities which are detected as 40%[77].

7.5 pH abnormalities in urine:

When high levels of acidic and alkaline conditions seen in patients' urine, indicated they are predisposed to calcium stone formers. During high levels of acidic conditions, urine will turn to become supersaturated by reacting with uric acid which participates in calcium oxalate stone formation[78].

7.6 Low urine volume:

Low urine volume is one of the important factors for stone formation. A high level of urine excretion helps to reduce the crystal to supersaturate but it is induced by the low volume of urine excretion. Many studies have reported that an adequate volume of water is important for preventing stone formation.

7.7 Unduly acidic urine:

Acidic urine condition denotes that urine has a low level of pH, which is detected as less than 5.5[79]. Acidic conditions in urine would be the result of increased production of endogenous acid and impaired ammonium excretion. This could also occur due to a rare genetic disorder known as hyperuricosuria[80,81].

7.8 Cystinuria:

Cystine stones are considered to be the main genetic disorder due to low cystine solubility in the urine environment[82], which is considered the least common type in adult stone formers but high prevalence in Children[83]. Reabsorption of defective renal tubular leads to the effect of other amino acids which include lysine, ornithine, and arginine.

7.9 Struvite stones:

High alkaline pH in urine is a suitable environment for infectious stone development. It is developed in the presence of organisms that can able to produce urease and it also turns to become supersaturated by reacting with phosphate magnesium and ammonium[84].

7.10 Drug-induced stones:

Certain drugs are one of the reasons for developing this rare form of stones. These drugs are differentiated into two groups, where the first group of drugs is poorly soluble with high urine excretion which leads to form crystal formation in urine (ex. triamterene). In recent studies, Scientists discovered that drugs that were used for HIV patients more frequently caused this type of stone (ex. indinavir and sulfadiazine). Another group of drugs will provoke the stone formation due to its metabolic activities[85].

8. Clinical manifestation:

Renal stones are hard deposits of minerals and compounds, where it develops in one or both kidneys. These stones travel through the ureter which carries urine from the kidney to the bladder and get excreted. Travel of renal stones depends on their size, where less than 5mm of stones is capable of passing through the ureter without causing pain but more than 5mm of stones are considered as critical size, which causes severe pain by their interaction with urethral wall. Larger stones can block the urine flow, this condition leads to cause urinary tract infections[86]. Usually, patients are advised to remove stones, when it is developed larger or responsible for any recurrent infections. The ureter has three narrowest parts in its structure which are known to be pelvic ureteric junction, mid-ureter, and uretero-vesicular junction (Fig 7). This Uretero-vesicular junction is the most common

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

site for obstruction. Usually, stone patients may feel severe flank pain which occurs sudden onset and becomes severe for 15 to 45 minutes, then it becomes intolerable with nausea and vomiting. Urinary frequency and painful urination may occur when stones are reached in the uretero-vesicular junction. Some stone patients may have painless haematuria[87].

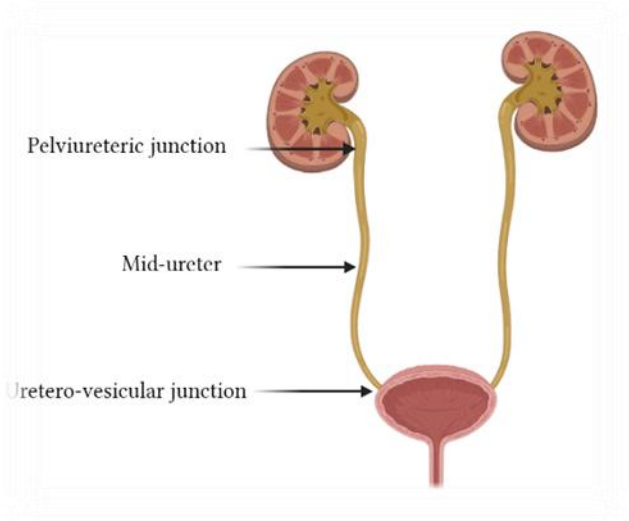

Fig: 7 The Anatomical site of the ureter has three parts which are known as the Pelviureteric junction, mid-ureter, and uretero-vesicular junction

Mohsen Akhavan Sepahi et al., in 2010 reported that haematuria, dysuria, fever, and pain were the most common clinical manifestations and symptoms of stone patients in children which is estimated at 56%[88,89.]

9. Treatment:

Treatment for renal stones depends on their size, type, and condition. Different types of treatments are described below.

9.1 Smaller stones:

Most of the smaller stones do not require any treatment, they will excrete in urine due to their smaller size. Sometimes doctors may suggest medical treatment to excrete stones.

Fluid intake:

stone formers are suggested to take more fluids intake. Borghi L, et al., in 1994 reported that increased water intake reduced the risk of supersaturation of urine with calcium oxalate (CaOx)[90]. Curhan cg et al., in 1998 discovered that an increased amount of citrus juice also reduced the risk for urinary supersaturation with CaOx[91]. Due to fructose content, some juices are not effective for stone reduction (ex: apple juice, grape juice)[92].

Diet:

Borghi et al., in 2002 reported that low levels of sodium, animal protein, and normal calcium intake helped the reduction of calcium stone recurrence[93]. This study disproved the statement of Hiatt RA et al., who conducted a test on renal stone patients and reported that a low diet in protein and fibers did not help with calcium stone recurrence[94].

Medical intervention:

Thiazide diuretic drugs are most commonly used in stone prevention and the most common drugs are hydrochlorothiazide, chlorthalidone, and indapamide. Other hand these drugs may lead to some side-effects in renal stone developers like weakness, weight loss, fatigue, and mental irritability [95].

Alkali treatment:

Potassium citrate is more common in recurrent calcium and uric acid stone formers which are given alone or combined with thiazide.

Bone loss and fractures are more common in urolithiasis patients which can be overcome by alkali and thiazide treatment[96].

Allopurinol treatment:

Ettinger B et al., in 1986 reported that allopurinol treatment showed good response in decreased level of urinary uric acid excretion along with stone recurrence[97].

Other treatment:

Barbey F et al., in 2000 reported that penicillamine and α- mercaptopropionylglycine showed decreased stone formations but these two drugs developed many side effects in patients[98]. The only approved drug for treating infectious stone formers is Acetohydroxamic acid[99].

Journal of Chemical Health Risks

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

9.2 Larger stones:

Critical-size stones are hard to excrete on their own, which will cause bleeding, damage to kidneys, and urinary tract infections. These conditions may require wide treatments and are described below.

Percutaneous nephrolithotomy (PCNL):

This is the first line of treatment for larger stones where this procedure is used to remove stones from the body when it is difficult to pass in urine. During this surgery, a small telescope and instrument will be inserted through a small incision in the back. Bleeding may occur during surgery.

Extracorporeal shock wave lithotripsy:

Based on the size and location of certain stones, doctors may suggest removing them by a certain procedure known as extracorporeal shock wave lithotripsy (ESWL). This ESWL is used to break the developed stones into many small pieces by using sound waves, later these smaller pieces can be passed out in urine[100].

Flexible ureteroscopy:

This is the standard treatment for stone patients when stones are estimated as less than 20mm in size[101]. During this treatment, doctors will pass a thin and flexible tube through the urethra and bladder, when stones are located they can break these stones into pieces and they will come out in urine later. This treatment has the lowest rate of complications compared to others[102].

10. Microbiome associated with renal stones:

10.1. Microbiome:

The intestinal microbiome influences urine composition, and this condition leads to the development of stones in the kidneys. The microbiome refers to the broad number of microorganisms that colonize the human body and develop complex communities. This community can lead to performing various biological processes by communicating with human host cells[103]. *Oxalobacter formigenes* is a gram-negative anaerobic bacterium that degrades oxalate in the intestinal tract and it also has the potential characteristics for the prevention of calcium oxalate stone formations. Falony G et al., in 2018 reported that oxalate-degrading bacteria such as *Oxalobacter formigenes*, *Porphyromonas gingivalis*, *Bifidobacterium sp*., and *Bacillus sp.* these bacteria are using oxalate as their carbon energy source, and develop in the presence of oxalate anion, reduced oxalate level in urine and it shows growth inhibition in crystallization of calcium stones in kidneys. There are multiple bacterial species are seen in the formation of stones and it is also contributed to urolithiasis[104]. Among all the five types, only struvite stones are considered to be infective stones. These stones are developed by urea-producing organisms, which break down urea to ammonia as the by-product resulting in increased urinary pH and facilitating struvite stone formation. The most common organisms isolated from this type of stone are *Proteus* spp., followed by *Staphylococcus aureus*, *Klebsiella spp., Providencia spp., Ureaplasma urealyticum* which are urease producers, and *Escherichia coli*, *Enterococcus spp*., are non-urease producer[105,106]. In recent years, bacteria have been recognized to contribute to struvite stone development but the role of bacteria in the development of the more common type of calcium-based stones has not been extensively investigated[107,108]. These calcium-based stones may become secondarily infected with urea-producing organisms. These organisms are present within the interspace of stones and antimicrobial agents are difficult to penetrate within the interspace, thus leading to a bigger stone formation where it causes blockage of the renal pelvis and ureter over weeks or months and ending up with complications such as persistent urinary tract infection (UTI), requiring long-term antibiotic treatment. Several studies reported that the association between bacteria in renal stones can lead to urinary tract infections (UTI) in urolithiasis patients[109].

10.2. Nanobacteria:

Nanobacteria (NB) are the smallest self-replicating organisms which is estimated as 60nm to 160nm in size[110]. Martel j et al., in 2004 stated that NB can also described as calcifying nanoparticles (CNPs), nanobacteria-like particles, and nanobes[111]. These nanobacteria can act as efficient mineralization to develop kidney stones[112]. Prevalence of these NB is increasing in urological disorders which includes kidney stone formation[113]. E. Garcia-Cuerpo et al., in

Journal of Chemical Health Risks

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JCHR (2024) 14(2), 1423-1439 | ISSN:2251-6727

2000 conducted a test on "Nanobacteria. An Experimental Neo-Lithogenesis Model," and reported that injected nanobacteria lead to developed stone formation in rats. Due to their smaller size compared to common bacteria, there is major criticism on NB that it is not considered as a sufficient living organism to contain all macromolecular compounds[114].

11. Future Prospects and Conclusion:

Understanding the intricacies of renal stones and their association with bacterial infection opens up promising avenues for future research and clinical practice. One potential area of exploration lies in the development of targeted therapeutic interventions aimed at mitigating the formation and progression of renal stones, particularly those linked with specific bacterial strains. Advances in imaging technologies and diagnostic modalities hold the potential to enhance early detection and intervention, thereby reducing the burden of renal stone-related complications. Additionally, further elucidating the underlying mechanisms of stone formation and microbial interactions can inform the development of novel preventive strategies and treatment modalities tailored to individual patient profiles.

In conclusion, this review underscores the multifactorial nature of renal stones and emphasizes the critical role of bacterial infection in their pathogenesis. By synthesizing current knowledge on renal stones, including classification, diagnostic methods, risk factors, and clinical implications, this study contributes to a comprehensive understanding of urolithiasis. Moving forward, continued research efforts aimed at unraveling the complex interplay between renal stones and bacterial colonization hold immense promise for improving patient outcomes and guiding evidence-based clinical management strategies in the field of urology.

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