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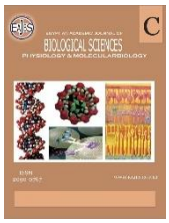

A Review of Types, Mechanisms, Complications, and Management of Renal Stone Formation

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ABSTRACT

Even though kidney stones seem to be one of the oldest disorders recognized by medicine, the exact processes by which they form and grow remain unknown. Significant progress has been achieved in our understanding of the pathophysiology of ten different types of stones, including the most common type, the idiopathic calcium oxalate stone former, thanks to the new digital endoscope and extensive renal physiological studies conducted on well-phenotyped stone formers. Based on our findings and those of others studying model systems, four distinct mechanisms for kidney stone formation have been proposed. It appears that the main way stones are formed in patients with hypercalciuria is by calcium oxalate crystals growing over Randall's plaque sites. In most stone phenotypes, overgrowths of the extremities of Bellini duct plugs have been observed; do these overgrowths lead to clinical stones? The cystinuric stone formers' microlith production appears to be limited to the lumens of their dilated inner medullary collecting ducts. Finally, it is suggested that cystinuric stone formers create their stones in free solution in the presence of several small, oval, smooth-looking calyceal stones that appear yellow. This article reviews the scientific evidence for these four different types of stone production and uses it to propose new areas of study. Moreover, it provided information on the pathology of kidneys, especially the different types of stone formation, mechanisms, complications, and management.

INTRODUCTION

The urethra, ureters, and kidneys make up the renal system. The kidneys' principal role is to filter about 200 liters of fluid daily out of the blood flow to the rest of the body, allowing for the outflow of metabolic waste, excess ions, and toxins while keeping vital substances in circulation (Treuting & Kowalewska, 2012). The kidneys are instrumental in maintaining a constant plasma osmolarity by controlling the concentrations of various electrolytes, solutes, and water in the blood. In addition to their role in maintaining acid-base balance over the long term, erythropoietin production, renin release, and vitamin D conversion to its active form, they also regulate blood pressure. (Ogobuiro & Tuma, 2019).

At the outset of urine generation, known as glomerular filtration, a passive process, is characterized by the energy-free passage of fluids and solutes through a membrane driven by hydrostatic pressure. The equilibrium between inward and outward forces within the capillaries dictates the filtration membrane's capacity to transport water and solutes (Holechek, 2003).

The volume of fluid filtered per minute, known as the Glomerular Filtration Rate (GFR), is affected by variables such as membrane permeability, accessible surface area for filtration, and net filtration pressure. To maintain and adjust GFR, both intrinsic and extrinsic regulatory mechanisms collaborate. A passive process known as glomerular filtration commences urine production by allowing hydrostatic pressure to drive fluids and solutes across a membrane without energy (Gaspari, Perico, & Remuzzi, 1997). The amount of water and solutes that penetrate the filtration membrane is determined by the interplay of outward and inward forces within the capillaries. To keep GFR in check, it is complexly controlled internally and externally. Removal of compounds bound to plasma proteins is the principal function of tubular secretion, which includes metabolites and pharmaceuticals (Nigam et al., 2015). Another important function of tubular secretion is the elimination of unwanted chemicals that have been passively reabsorbed, such as urea and uric acids. In addition, the aldosterone hormone plays a crucial role in regulating excess potassium removal at the collecting duct and distal convoluted tubules, an essential aspect of tubular secretion (Laasya, Thakur, Poduri, & Joshi, 2020).

The Pathology of The Renal System:

Pathologies of the renal system exhibit a diverse array of clinical presentations, including:

1. Emphysematous Urinary Tract Infection (UTI):Gas formation is a hallmark of emphysematous UTIs in lower or upper urinary tract infections. *Klebsiella sp.* and *Escherichia coli* are common culprits, but other species like *Proteus, Enterococcus, Pseudomonas, Clostridium,* and *Candida* spp. It could be at play as well. A common way to identify patients at increased risk is by looking for signs of diabetes and urinary tract obstruction. Symptoms such as nausea, vomiting, fever, chills, flank or abdominal pain, and pyelitis, cystitis, or pyelonephritis are common clinical manifestations (Weintrob & Sexton, 2010).

2-Chronic kidney disease (CKD)*:* Deterioration of kidney function over an extended period characterizes CKD, which can strike suddenly within months or creep up over many years. The various components of the kidneys, such as the vasculature, glomeruli, and tubulointerstitium, are affected by various causes of CKD, including immunological, toxic, metabolic, and other factors (Levey & Coresh, 2012). In each of the five stages of CKD, the glomerular filtration rate (GFR) gradually decreases. Early symptoms are not always specific enough to diagnose correctly; later on, tests like glomerular filtration rate estimation albuminuria determination, and even kidney biopsy can confirm the diagnosis (Kalantar-Zadeh, Jafar, Nitsch, Neuen, & Perkovic, 2021). People with preexisting diseases like diabetes, obesity, atherosclerosis, or hypertension often experience renal circulatory impairment, which causes a progressive and irreversible loss of function. Edema and hypertension are typical clinical manifestations, but it is important to note that some patients may not experience any symptoms at all (Webster, Nagler, Morton, & Masson, 2017).

3-Urinary Incontinence*:*There are four primary forms of urinary incontinence, defined as the involuntary loss of urine: urge, stress, mixed, and insufficient bladder emptying. Men and women share some commonalities and have some distinct differences when it comes to the causes of these types. Between eleven percent and thirty-four percent of men over the age of 65 suffer from urine incontinence (Norton & Brubaker, 2006). Age, prostate-related issues, a history of UTIs, neurological disorders, diabetes, and other chronic diseases are the main risk factors (Lee & Kuo, 2017). Factors that increase a woman's risk include getting older, being overweight, having more children than average, and the way they give birth (Kulie *et al.*, 2011) (reference needed). Properly diagnosing and treating urinary incontinence requires understanding the

unique elements causing the condition in both sexes (Luber, 2004).

4-Nephrolithiasis: The formation or presence of mineral deposits, often called calculi or stones, inside the urinary tract can lead to a condition called urolithiasis. The three main types of this condition are nephrolithiasis, ureterolithiasis, and cystolithiasis, depending on where the stones are located: in the kidneys, the ureter, or the bladder respectively.

Pediatric urolithiasis is the medical term used when the condition appears in a person younger than 18 years old (Luber, 2004). In 80% of cases of nephrolithiasis, the kidneys contain stones made of crystallized calcium, magnesium, cystine, or uric acid. The most prevalent kind of calcium stone is calcium oxalate, but calcium phosphate is also present (Pfau & Knauf, 2016). An elevated risk of chronic and end-stage renal disease is linked to this condition. There are several things that can put you at risk for developing nephrolithiasis. These include eating a lot of oxalate, having the condition in the past, having a family history of it, getting UTIs often, and having your intestines absorbed more oxalate as a result of gastric bypass, bariatric surgery, or short bowel syndrome. A substantial dietary risk factor for urolithiasis is the composition of the diet, especially inadequate fluid consumption (Pfau & Knauf, 2016).

Kidney Stones:

Kidney stones are hardened mineral deposits that can be found in the pelvis and renal calyces, either on their own or attached to the renal papillae. When minerals in urine become too concentrated, these stones which contain both organic and crystalline components form (Priante *et al.*, 2017). Most kidney stones consist of calcium oxalate, which forms on the surface of the renal capillaries on a bed of calcium phosphate called Randall's plaques. An extremely high percentage of people experience stone formation (14.8 percent), with a recurrence rate of up to 50 percent within the first five years following the initial episode (Khan *et al.*, 2016).

Stones Types and Causes:

Abnormalities in the composition of urine chemicals determine the chemical composition of kidney stones. There are differences in the underlying pathogenesis and variations in the chemical composition (mineralogy) that cause these stones to display size, shape, and variation in form (Fig. 1)(Chadha, Garg, & Alon, 2001). Kidney stones are typically categorized into five types, as outlined below.

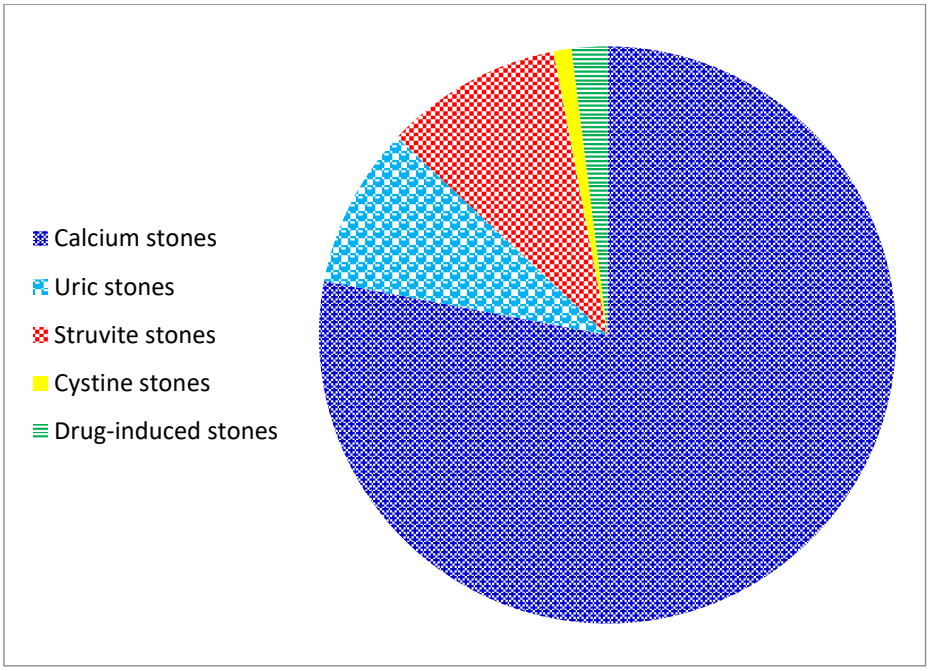

Fig. 1: Shows the distribution of different types of stones (Chadha *et al.*, 2001)

1-Calcium Stones:The vast majority of kidney stones are calcium stones, which account for about 80% of all calculi in the urine. The composition falls into this category and includes a mix of 50% pure calcium oxalate (CaOx), 5% calcium phosphate (CaP), and 45% both (Meyers, 2020).

According to Parvinzadeh et al., (2013) and illustrated in Figure 1, the main ingredient of calcium stones is either hydroxyapatite or brushite, which is also known as calcium hydrogen phosphate. According to Al-Atar et al. (2010), calcium oxalate, whether in monohydrate, dihydrate, or a mix of the two forms, makes up more than 60% of kidney stones. Calcium oxalate (CaOx) stones can form for a variety of reasons. Hyperuricosuria, hyperoxaluria, hypocitraturia, hypomagnesuria, and hypercystinuria are listed among these (Das, 2019). Hypercalciuria can be caused by resorptive, renal leak, absorptive, or metabolic diseases. Calcium oxalate (CaOx) stones are more likely to form in urine with a pH between 5.0 and 6.5, whereas calcium phosphate stones are more likely to form in urine with a pH higher than 7.5. When compared to other kidney stone types, calcium stones are more likely to recur (Goldfarb, 2012).

2-Struvite or Magnesium Ammonium Phosphate Stones:Infection stones, urease-producing struvite stones, or triple phosphate stones are common in patients with chronic UTIs. Although *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Enterobacter* sp. are less prevalent, *Proteus mirabilis* is typically the main culprit (Michel Daudon et al., 2022). An increase in urine alkalinity and a pH greater than 7 are the results of urea's breakdown into ammonia and carbon dioxide, a process in which urease is essential. The insoluble ammonium products are covered with phosphate because of their lower solubility at alkaline pH compared to acidic pH. Big staghorn stones are made when this procedure is completed. Struvite stones are more common in women than in men. Specifically, according to (Deviney, 2018)., Escherichia coli cannot cleave urea and is not linked to the production of struvite stones.

3-Uric Acid Stones or Urate:A low urinary pH (pH < 5.05), decreased urine volume, and hyperuricosuria can be caused by a diet rich in purines, particularly animal proteins such as meat and fish. Uric acid stones are more likely to form when these two factors are combined (Lemann *et al.,* 1996). Kidney stones can form in some people who suffer from gouty arthritis. Uric acid nephrolithiasis is more common in males than in women and is typically caused by unknown factors (Alelign and Petros, 2018).

4-Cysteine Stones:When it comes to hereditary causes of kidney stones, cystinuria is by far the most common. A hereditary defect in the reabsorption of filtered cystine by the proximal tubules causes cystine nephrolithiasis to recur when there are excessive amounts of this insoluble amino acid in the urine (Dahlem, 2014). Cysteine either leaks out of the kidneys or is not absorbed properly due to the genetic abnormality. Cysteine builds up and forms stones because it is insoluble in urine. According to Gubler (2014), people who are homozygous for cystinuria have the ability to excrete over 600 millimoles of insoluble cystine every day.

5-Drug-Induced Stones:About 2% of all calculi in the urinary tract are drug-induced kidney stones. Medications in this category typically belong to one of two groups: those that cause metabolic changes favorable to the development of urinary stones, and those that have a high renal excretion and low urine solubility (Daudon *et al.,* 2018). Medications and their byproducts make up the first type of calculi, while the second type of drugs aid in the production of calcium and/or uric acid stones (Sohgaura & Bigoniya, 2017).

Medications that are not very water-soluble and which cause a lot of crystallization in the urine make up the first group. Interestingly, sulphadiazine, which is used to treat cerebral toxoplasmosis, and atazanavir, which are protease inhibitors used to treat human immunodeficiency virus (HIV), are

often mentioned as potential factors. Furthermore, nephrolithiasis can be caused by around twenty other molecules, including ceftriaxone or preparations containing ephedrine when taken in large quantities or for long periods of time (Raheem *et al.,* 2012).

Medications that alter the metabolism of the urine and cause the excretion of certain purines (such as calcium, phosphate, oxalate, citrate, uric acid, etc.) are categorized into the second group and are known to cause calculi to develop in the urinary tract. Patients taking carbonic anhydrase inhibitors such as acetazolamide or topiramate, or those who take calcium and vitamin D supplements without medical supervision, are at increased risk of developing metabolically induced stones (Hess, 1998).

Mechanisms of Renal Stone Formation:

Supersaturation of urine and physicochemical changes define the biological process of renal stone formation. In a supersaturated state, the amount of dissolved matter in a solution exceeds what the solvent is normally capable of holding (Kavanagh, 2010). In situations where there is an excess of solutes in the urine, a process called nucleation begins, and eventually, crystal concretions are formed. When the concentration of two ions in a solution surpasses their saturation point, crystallization occurs (Wang & Nancollas, 2008).

Phosphorus and particular concentrations of excess substances affect the phase transition from liquid to solid. The degree of urinary saturation determines the risk factors for crystallization, which include elevated levels of stone-forming constituents such as calcium, phosphorus, uric acid, oxalate, cystine, and low urine volume (Rosés, 2004). Both thermodynamics and kinetics play a role in crystallization in a supersaturated solution. The former controls nucleation, while the latter determines the rates of crystal growth. Therefore, the best way to avoid lithiasis is to keep the water from becoming too saturated (Kim, 2021). Keep in mind that the ratio of urinary inhibitors to crystallization promoters is the primary determinant of stone formation (Fig. 2).

The mineral phase of stone formation is the same for all types of stones. The process that ultimately results in the formation of stones, however, differs from one kind of stone to another and from urine chemistry to urine chemistry. Supersaturated urine, especially at low inhibitor concentrations, can cause the crystallization of calcium-based stones such as calcium oxalate or calcium phosphate. The formation of calcium oxalate stones can be accelerated when uric acid disrupts the solubility of calcium oxalate. According to Khan et al. (2016), inhibitory substances can prevent stones from forming in people who do not have any problems with them.

Stones develop when crystals undergo nucleation, growth, aggregation, and renal retention (Alelign & Petros, 2018).

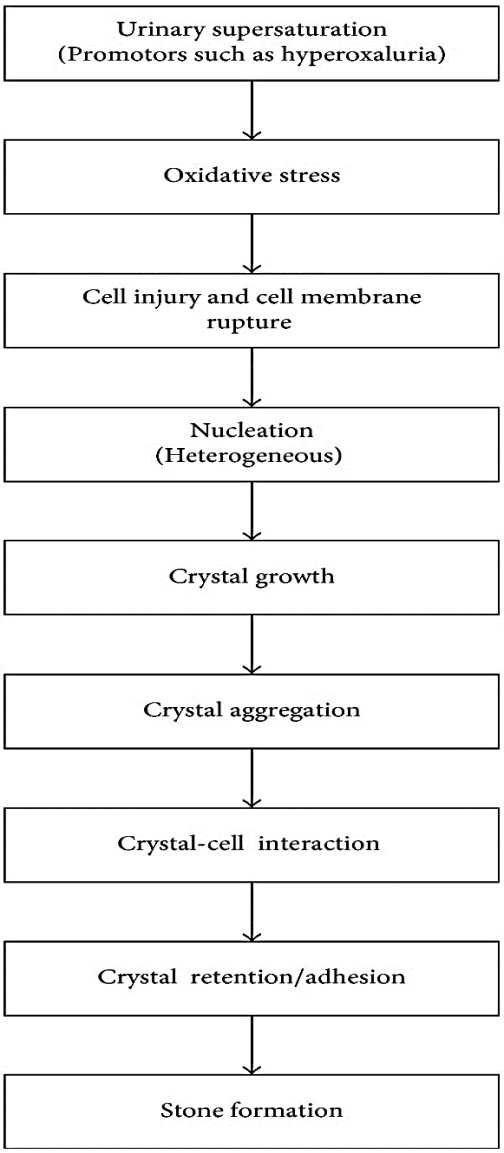

Fig. 2: Summary of the various steps involved in kidney stone formation (Alelign & Petros, 2018).

Stones Complications:

When kidney stones block blood flow, they can cause a host of problems (Khan *et al.*, 2016). Serious infections, such as potentially fatal septicemia (blood poisoning), renal function loss from prolonged blockage, abscess formation, urosepsis, and urinary fistulas are among these complications. Chronic kidney disease can cause scarring in the kidneys and, in the worst-case scenario, permanent kidney failure. Nephrectomy, the surgical removal of the kidneys, may be required in extreme cases of renal failure. Furthermore, unpleasant urinary retention and bladder obstruction can result from a big kidney stone passing into the bladder and becoming stuck in the urethra (Basavaraja, 2006).

Risk Factors:

Factors that increase the likelihood of developing a stone in the urinary tract include but are not limited to, one's age, gender, race/ethnicity, diet, amount of water consumed, geographic region, time of year, and health conditions. Yongzhi *et al*. (2018) found that the risk of urinary tract stones in children was more than three times higher in those whose parents had the condition. Stones can form as a result of a diet that is deficient in water, high in vitamin D and dairy

products, and heavy in salt, refined carbs, and animal protein. The formation of calcium oxalate crystals is enhanced when there is an increase in the absorption of enteric oxalate, which is commonly linked to malabsorption (D'Alessandro *et al.,* 2019). Struvite crystals can be formed when the urinary pH is altered by urease-producing bacteria, which can happen in urinary tract infections. Low fluid intake and a family history of diabetes, obesity, gout, or hypertension are additional risk factors. In addition, when there is chronic diarrhea and the urine has an acidic pH (<5.5), the formation of uric acid is promoted (Stroup & Auge, 2010).

Management of Stone Formation:

According to McClinton *et al.* (2020), interventions like percutaneous nephrolithotomy, ureteroscopy (both rigid and flexible), or shock wave lithotripsy are frequently required for kidney stones bigger than 6 mm. Determining and treating the root causes is crucial for preventing kidney stones. To effectively manage this condition, one must make dietary changes and take medication to prevent the formation of stones, both initially and again. According to Ahn and Harper (2021), nutritional management is the most effective strategy for preventing urolithiasis because it is a cost-effective public health measure that has a significant societal impact.

To reduce urine saturation and dilute factors that promote calcium oxalate crystallization, it is essential to drink enough fluids (Sromicki & Hess, 2020).In contrast, because sodium reduces renal tubular calcium reabsorption and increases urinary calcium levels, an increase in sodium consumption increases the risk of stone formation. A decrease in citrate levels, an increase in urinary calcium excretion through bone reabsorption, and a decrease in urine pH can result from an increase in protein consumption (Heilberg & Schor, 2006). Kidney stone formation may be affected by these dietary factors, which have a major impact on urine chemistry.

By binding dietary oxalate in the gastrointestinal tract and reducing its absorption, calcium supplements may be able to alleviate this effect. You should try to alkalize your urine if you want to prevent calcium oxalate, cystine, and uric acid stones. Fruit and vegetable diets, citrate supplements (over-the-counter or prescribed), and alkaline mineral waters can all help achieve this goal. which are all involved in keeping urine alkaline (Hesse, 2009).

Because of their high sulfur-containing amino acid content, animal proteins add to an elevated acid load, so it's recommended to limit their consumption as well. In turn, this causes a decrease in citrate levels, an increase in urinary calcium excretion due to bone reabsorption, and a decrease in urine pH (Barzel & Massey, 1998). It is now known that people who are prone to kidney stones shouldn't be advised to limit their calcium intake unless there is proof of excessive calcium consumption. This is in contrast to the traditional advice that people prone to calcium stone formation should avoid dairy products and other foods rich in calcium (Park & Pearle, 2007).

The risk of stone formation increases because the intestinal absorption of oxalate is increased when calcium intake is reduced. Supplemental calcium may bind dietary oxalate in the gastrointestinal lumen, which may decrease its absorption. Nevertheless, there is some disagreement regarding the benefits of taking calcium supplements. Because ascorbic acid converts to oxalate in living organisms, vitamin C has been associated with stone development. Hence, it is advised to cut back on vitamin C supplements (Straub, 2007).

In order to avoid calcium oxalate (CaOx), cystine, and uric acid stones, it is possible to alkalize the urine by eating a lot of fruits and vegetables, taking citrate supplements, or, as prescribed, drinking mineral waters with a high pH. People who are susceptible to cystine stones should limit their protein and sodium consumption, while those who are prone to uric acid stones must take gout management very seriously. The most common way to prevent struvite stones is to acidify the urine (Peerapen &

Thongboonkerd, 2023).

Conclusion:

The formation of renal stones, also known as nephrolithiasis, is a more complex and potentially harmful issue in renal pathology. A lack of water intake, excessive or insufficient physical activity, obesity, bariatric surgery, or a diet high in salt or sugar can all lead to kidney stones. For some, infectious diseases and family history may play a significant role. Recurrence prevention requires consistent follow-up and changes to one's way of life. The stone's type, size, and patient history determine the treatment plan.

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