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An Update on Kidney Stone: Review

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Abstract: ***Kidney stone disease is the term for a crystalline stone that often develops within the kidneys. It is an increasingly common urological disease that affects about 12% of people worldwide. A higher risk of end - stage renal failure has been linked to it. Though there are many different types of kidney stones, calcium oxalate stones are the most prevalent kind. Renal papillary surfaces are affected by Randall's plaques. The complex process of urinary stone formation is influenced by a multitude of physicochemical processes, such as supersaturation, nucleation, development, aggregation, and retention of urinary stone components within tubular cells. These phases are impacted by an imbalance between the components that either promote or prevent urine crystallisation. Additionally, research has shown that cellular injury causes increased particle retention in kidney papillary surfaces. When oxalate comes in contact with renal epithelial cells, they initiate a series of events that result in programmed cell death through p38 mitogen - activated protein kinase pathways. At the right time, kidney stones cannot be cured, nor can they be kept from coming back. Research on the process of kidney stone formation is necessary to create new drugs for the treatment of urolithiasis. Thus, the aim of this study was to collect the latest data on the etiology, pathophysiology and preventive strategies of kidney stones.***

Keywords: kidney stones, calcium oxalate, crystallisation, urolithiasis

1. Introduction

1.1. Kidney Stones

Kidney stones often lodge in one or more kidneys.[1] Since 4000 B. C., mankind has been plagued with urinary tract stones, the most common ailment affecting the urinary system. One of the biggest concerns for human health today is preventing the recurrence of kidney stones. A deeper understanding of the mechanics underpinning stone formation is necessary to avoid the recurrence of stones.[2] End - stage renal failure and kidney stones have been associated, diabetes, hypertension, cardiovascular problems, and chronic kidney illnesses. Kidney stones have been proposed as a systemic illness associated with the metabolic syndrome. If there is nephrocalcinosis and nephrolithiasis are related, then 2–3% of end - stage renal patients have this condition.[3]

The location of kidney stones inside the kidney, ureter, or bladder affects the symptoms that accompany them. Stone formation may not cause any symptoms at first. Following this, people may have symptoms including severe cramping (renal colic), pain in the flanks or back, blood in the urine, kidney dilatation (hydronephrosis), obstruction of the urine flow, and urinary tract infections. In addition to the pain caused by the stone occurrence, these situations may also result in nausea and vomiting. Both the individual's quality of life and the GDP of the nation are greatly impacted by the related expenses of treatment and the time missed from work.[4]

1.2. Kidney stone epidemiology

Kidney stone illness is becoming more common and more likely to reoccur internationally, despite the lack of effective treatment options. Approximately 12% of people worldwide may get urolithiasis at at some time throughout their existence. It affects individuals of all ages, genders, and ethnicities; however, among those in the 20–49 age range, men are more likely than women to experience it. The predicted relapse rate of secondary stone forms in patients who do not employ metaphylaxis is 10–23% annually, in ten years, 49.99%, and in twenty years, 76%. Men had a higher lifetime recurrence rate of nephrolithiasis, despite the condition being more common in females. Therefore, the therapy of urolithiasis requires a strong emphasis on preventive measures.[5]

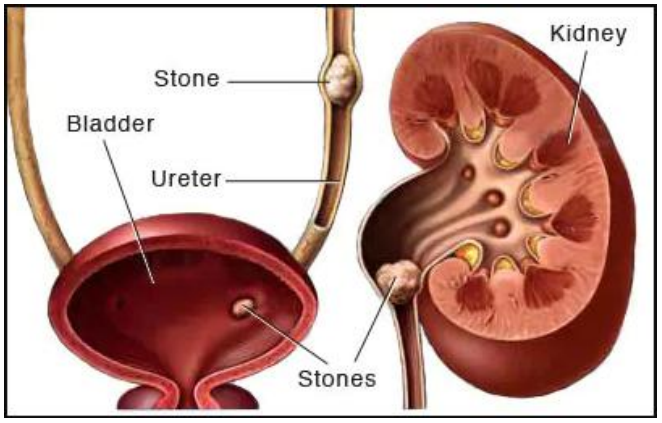

Figure 1: Locations of kidney stones in the urinary system

According to recent research, both in industrialised and developing nations, the frequency of urolithiasis has increased over the last several decades.[6] This increasing tendency is thought to be related to dietary and lifestyle modifications including inactivity and global warming. One in eleven Americans suffer from kidney stones, while an estimated 600, 000 Americans have urinary stones annually. Urinary stones are expected to affect 13% of Indians, and 52% of those individuals may lose their ability to function as kidneys.[7]

2. The Stone and Urinary System

Urine iontrate is produced in the glomerulus and enters the tubules where it undergoes changes in secretions or reabsorption the substance's volume and composition. While

the collecting ducts and distal tubules control small changes in urine composition, the proximal tubules are essential for most solute reabsorption.[8] Urine is concentrated via the Henle loop and is composed of 96% water, 2.6% urea, and 2.6% of a mixture of minerals, salts, hormones, and enzymes. Reabsorbing water, glucose, salt, chloride, bicarbonate, and other necessary components including proteins, amino acids, calcium, phosphate, and potassium, the proximal tubules return these substances to the circulation. The blood's salt and acid - base balance are controlled by the distal tubule.[9]

3. Type of Kidney Stone

The anomalies in urine composition of different substances determine the elements that make up kidney stones. Stones differ in terms of shape, size, and chemical composition (mineralogy). Five categories are often used to categorise kidney stones according to differences in the origin and mineral content of each.[10]

3.1 Calcium Stone

About 81% of all urinary calculi are calcium stones, the most common kind of kidney stone. Calcium stones may include either pure calcium oxalate (CaOx) (49.90%), calcium phosphate (4.99%), or a mixture of the two (46%). Brushite, also known as hydroxyapatite or Calcium stones mostly consist of calcium hydrogen phosphate.[11]Kidney stones are mostly composed of calcium oxalate and may be found as CaOx monohydrate, CaOx dihydrate (COD, also known as weddellite, $CaC_2O_4 \cdot 2H_2O$), or in more than 60% of instances.[12]

Figure 2: Calcium Stone

Many conditions include hyperuricosuria, hyperoxaluria, hypocitraturia, hypomagnesuria, hypercystinuria, and hypercalciuria that may lead to the production of CaOx stones.[13] Calcium phosphate stones often form at pH levels greater than 7.5, while CaOx stones are more likely to occur in urine with a pH range of 5.0 to 6.5. Compared to other forms of kidney stones, calcium stones have a higher recurrence rate.[14]

3.2 Magnesium Ammonium Phosphate or Sturvite Stones

Roughly 10–15% of people have struvite stones, sometimes known as triple phosphate and infectious stones. Individuals suffering from persistent urinary tract infections (URE - producing bacteria) such as Enterobacter, Pseudomonas aeruginosa, and Klebsiella pneumonia are more likely to have it. Urine's pH is raised (usually more than 7) when urea is split or cleaved into ammonia and CO2. Urease is required for this process. A sizable staghorn stone development results from Because phosphate is less soluble at alkaline pH levels, it precipitates on insoluble ammonium compounds than it is at acidic pH values. This kind of stone is more common in women than in males. Escherichia coli is not linked to struvite stones and is not able to breakdown urea.[15]

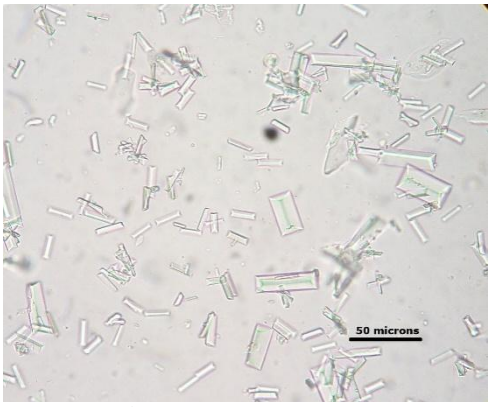

Figure 3: Struvite Stone

3.3 Urate or Uric Acid Stones

This represents three to ten percent of all stone varieties. Diets high in purines, especially those including meat and fish, might worsen the formation of uric acid stones by causing low urine pH (pH <5.05), hyperuricosuria, and decreased urine volume.[16] People who have gouty arthritis may develop kidney stones. Males are more prone than females to develop uric acid stones, and the most common cause of uric acid nephrolithiasis is idiopathic uric acid nephrolithiasis.[17]

Figure 4: Uric Acid Stones

3.4 Cystine Stones

These stones make up less than 2% of all stone types. It is a genetic disorder that affects how amino acids and cystine are transferred. An overabundance of cystinuria in urine excretions is the result of an autosomal recessive illness brought on by a chromosome 2.[18] mutation in the rBAT gene Deficit leads to decreased absorption of cystine. via the renal tubules or cystine leakage into the urine. It causes cystine stone formation and does not dissolve in urine. The formation of cystine in the urine is the sole clinical indication of this cystine stone illness. Over 600 millimoles of insoluble cystine are excreted daily by those homozygous for cystinuria.[19]

Figure 5: Cystine Stones

3.5 Drug - Related Stones

This makes up around 1% of all stone types. Medication such as guaifenesin, triamterene, atazanavir, and sulfa medicines may cause these stones. Kidney stones may occur in patients using indinavir sulphate, a protease inhibitor used to treat HIV infection.[20] Such lithogenic drugs or the byproducts of them may settle on pre - existing renal calculi or produce a nidus. However, Certain drugs may lead to the development of calculi via their metabolic activity by interfering with the metabolism of purines or calcium oxalate.[21]

4. Kidney Stone Formulations

Urinary stones consist of both crystalline and noncrystalline phases as well as organic material, which is known as the matrix. The macromolecules proteins, lipids, carbohydrates, and glycosaminoglycans (GAGs) comprise the organic matrix of kidney stones. These compounds possess a notable impact on the processes involved in kidney stone production by either stimulating.[22]Proteins (65%), nonamino polysaccharides (9.7%), hexosamine as glucosamine (5.20%), water (10.30%), and inorganic ash (10.50%) make up the majority of the stone matrix's constituents. The kidney stone generation process is mapped out by the matrix. Phospholipids comprise around 10.3% of the matrix of the stone, or 8.6% of all the lipid in the matrix of all stones. The organic matrix's phospholipids found in cell membranes encourage the development of calcium oxalate and calcium phosphate stones. The primary ingredient in the matrix of many stones is albumin.[23]

Stones affect 25% of those with calcium phosphate (CaP) that include brushite, an increasingly prevalent hard phosphate mineral. The urinary system may include brushite, or calcium monohydrogen phosphate dihydrate, which is a form of calcium phosphate (CaP), CaHPO4·2H2O), hydroxyapatite, or carbonate apatite. Brushite is not susceptible to ultrasonic lithotripsy or shock wave therapy.[24]

Etiology of Kidney Stones

Calculogenesis, the process by which kidney stones develop, is complex and multidimensional. It involves factors that are both intrinsic (such age, sex, and inheritance) and extrinsic (like location, food, mineral makeup, and water consumption) a review of the possible causes of kidney stones.[25]

5. Mechanisms of the Formation of Renal Stones

The biomineralization or pathogenesis of kidney stones is An intricate biological mechanism that remains mostly enigmatic. Urine supersaturation and physicochemical alterations are two biological processes that lead to renal stone development.2[6]If there is more dissolved material in a solution than the solvent could ordinarily dissolve, the solution is said to be supersaturated.[27] Specific concentrations of excess chemicals and pH have an influence on the change from a liquid to a solid state. Risk factors for crystallisation include low urine volume and insufficient urinary saturation with regard to the elements that form stones—calcium, phosphorus, uric acid, oxalate, and cystine.[28] The dynamics of the supersaturated solution, which include the rates of nucleation and crystal growth, govern the crystallisation process, and thermodynamics, which causes nucleation. Therefore, staying away from supersaturation may help prevent lithiasis.[29]

However, the steps involved in the creation of stones vary according to the kind of stone and the urine's chemical composition. For instance, stones composed of calcium may crystallise in supersaturated urine when inhibitor concentrations are low.[30]Uric acid causes calcium oxalate to become less soluble, which promotes the formation of CaOx stones. Stone formation is the result of a series of processes that include the kidneys' crystals' nucleation, development, aggregation, and retention. Drugs that make it safe suppress the crystallisation process in healthy controls.[31]

5.1 Crystal Nucleation

The creation of a kidney stone begins with the nucleus, also known as a nidus. It is produced by urine that has become supersaturated and is held inside the kidneys.[32] Free atoms, ions, or molecules begin to assemble into small clusters in a supersaturated liquid. When the bulk free energy of these clusters is lower than the liquid's, precipitation occurs. For example, insoluble calcium oxalate crystals may be created when charged soluble molecules like oxalate and calcium interact. The kidney may generate nucleation by either an ixed particle or free particle mechanism. Nucleation begins in supersaturated fluids when promoters surpass inhibitors.[33]

A lower chemical pressure than that needed to form the original nucleus may be used for crystallisation when a nucleus is formed and/or anchored. Heterogeneous

nucleation is the mechanism by which nuclei are created.[34] Through promoting heterogeneous nucleation and crystal aggregation, mucopolysaccharide functions as a binding agent in the organic matrix. However, it is said that nanobacteria create apatite structures that operate as a crystallisation centre to build stones. The whole process accelerates the production of stones. Current study is being done on the function of oxalated - degrading bacteria, namely Oxalobacterformigenes, in the creation of CaOx stones. One of the finest methods to manage kidney stones is to use a therapy that focuses on the nucleation intervention process.[35]

5.2 Crystal Growth

Urine crystals adhere to one another to create crystal growth, a tiny, hard mass of stone. assembling premade Advances in Urology crystals or thereafter causing a crystal to nucleate on the surface covered with matrix are the two methods used to achieve stone growth. The development of stones clogs the renal tubules more slowly and gradually. The surface energy increases the cluster's total free energy after a nidus is attained. This is accomplished by adding additional crystal components to the nidus' surface.[36] The two primary organic matrix components that encourage the production of CaOx stones are osteopontin and Tamm - Horsfall protein. In vitro studies using crystals made from human urine showed a tight connection between the organic matrix and the crystals that contained calcium. (lipids and proteins). It is essentially thought that lipids found in cellular membranes play a role in crystal nucleation.[37]

5.3 Crystal Aggregation

Aggregation is the process by which a hard, tiny mass of a crystal in solution clings to one another to one another to create a bigger stone. It is acknowledged in any model of CaOx urolithiasis that exhibits crystal aggregation most likely plays a role in the kidneys' ability to retain crystals. The process of crystal aggregation is thought to be the most crucial in the process of making stones.[38]

5.4 Crystal - Cell Interaction

Crystal retention, often referred to as crystal - cell contact, is the process by which growing crystals adhere to the epithelial cells lining the renal tubules. Exposure to sharp calcium oxalate monohydrate (COM) crystals in individuals suffering from hyperoxaluria or high oxalate concentrations resulted in damage to renal tubular epithelial cells. Crystals migrate from the basolateral side of cells to the basement membrane due to crystal - cell contact.[38] It is feasible for crystals to cling to the basement membrane of the kidney and become incorporated into cells. One important first stage in the development of nephrolithiasis may be the contact of Renal epithelial cell surface COM crystals. The heightened retention force between the crystal and the injured renal tubule epithelial cells promotes CaOxcrystallisation. Urine is assumed to be released when lysosomes and/or macrophages within the cells break down most crystals linked to epithelial cells.[39]

Research done in vitro and in vivo has shown that a multitude of membrane vesicles that function as calcium crystal nucleators are produced as a consequence of cellular breakdown after renal tubular cell injury. Chemicals secreted by wounded cells, such as Crystal agglomeration is caused by anionic proteins such as renal prothrombin fragment - 1. One of the possible causes of renal cell damage is reactive oxygen species. Reducing renal oxidative stress may prove to be a successful therapeutic approach.[40]

The cell membrane of injured cells potentiates to invert, acting as a site of crystal adhesion and being anionic to the urine environment. When it comes to attachment strength to COM crystals are better than calcium oxalate dihydrate (COD) crystals because of the inverted anionic membrane. On the other hand, binding molecules like COM crystal adhesion of hyaluronan on Madin - Darby canine kidney epithelial cells may be the reason of preferential difference.[41]Controlling crystal - cell retentions is one of the most effective approaches to treat urolithiasis, despite the fact that the precise processes behind crystal - cell interaction are yet unknown.[42]

5.5 Endocytosis of CaOx Crystals

Kidney stones develop first by a process called endocytosis, which is the renal tubular cells' absorption of crystals. Studies on the interaction between tissue culture crystals and cells have shown that COM crystals internalise after adhering fast to microvilli on the cell surface.[43] Crystals may be coated with polyanion molecules, such as citrate, glycosaminoglycans, and glycoproteins, which are present in tubular urine and urine and which prevent COM crystals from sticking to cell membranes. For instance, there are two biological roles for Tamm - Horsfall glycoproteins (THP) in the development of stones.[44] According to Lieske et al., THP may encourage the development of renal stones by starting the interaction between COM crystals and the nephron's distal tubular cells. According to a different research, THP's viscosity rises when ionic strength is increased and pH is lowered. This indicates that THP has a strong potential to polymerize but is unable to hinder crystallisation.[45]

Moreover, THP becomes an effective crystallisation promoter in the presence of additional calcium ions. On the other hand, according to Hess, THP is believed to prevent the development of COM stones by preventing COM aggregation at reduced ionic strength and high pH.4[6] Normal THP inhibited COM aggregation, whereas Desialylated THP increased it, according to COM aggregation experiments. According to related research, uromodulin may encourage THP may stop crystals of calcium oxalate accumulating. When the mouse embryonic stem cells' THP gene is deactivated, calcium crystals spontaneously grow in adult kidneys, indicating that THP is a necessary urine inhibitor for nephrolithiasis in humans.[47]

When stones develop, a number of cellular and extracellular processes are involved. One possible way to prevent the formation of stones would be to use modulators that target the stages from supersaturation to crystal retention.[48] Similarly, another strategy to stop the development of stones would be to limit the expression of crystal - binding

molecules on epithelial cell membranes, as monocyte chemoattractant protein - 1, osteopontin, sialic acid, and hyaluronic acid. Research has shown that the onset of oxidative stress and reactive oxygen species (ROS) are the main factors that lead to stone calcification.[49] Research carried out both in vitro and in vivo have shown that renal epithelial cells are vulnerable to damage by CaOx crystals, which may result in renal cell death. The process of urinary stone development is not well understood. In a similar vein, being subjected to hypercalciuria increases the formation of calcium oxalate by damaging cells and causing ROS - induced lipid peroxidation. An overview of the several processes that go into making stones.[50]

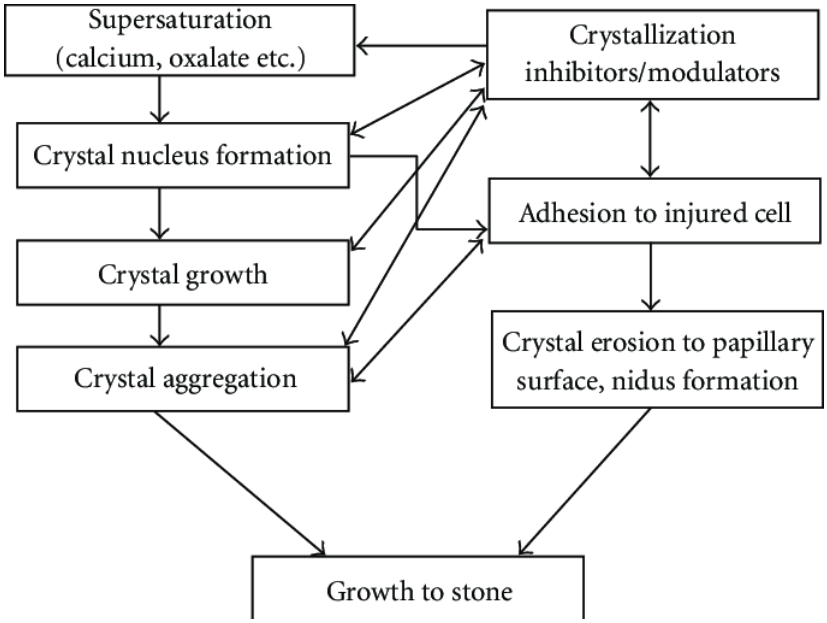

Figure 2: Kidney stone formation

5.6 Cell Injury and Apoptosis

High concentrations of oxalate or CaOx crystal exposure cause damage to the epithelium, which increases the risk of future stone formation. Proteins that might trigger inflammation are expressed and synthesised more often when CaOx crystals are deposited in the kidneys.[51] Crystals may go to the interstitium or be endocytosed by cells. According to one theory, damaged cells produce a nidus that helps particles stay on the surface of the renal papillaries. Crystals attach themselves to damaged renal tubular cells in patients with severe primary hyperoxaluria. Lysosomal, prostaglandin E2, and cytosolic enzyme release were all increased by the augmentation of Madin - Darby canine kidney (MDCK) cell lines with calcium oxide crystals.[52]Large - scale injections of CaOx crystals or oxalate ions seem to be dangerous because they may destroy renal tubular cells, according to a research conducted on animal models. It has been proposed that oxalate inhibits the enzymes responsible for breaking down free radicals, thereby increasing their availability. Reactive oxygen species, for example, have the ability to degrade the transmembrane potential of the mitochondrial membrane. These procedures are acknowledged as being at the beginning of the apoptotic process.[53]

The production of some substances is regulated by the p38 MAPK (p38 mitogen - activated protein kinase) signalling pathway being activated. Pro - inflammatory cytokines have the ability to activate p38 MAPK, which subsequently phosphorylates and activates transcription - related variables. Gene expression in renal cells alters in response to oxalate exposure, initiating signalling cascades that lead to apoptosis.[54] According to a research, exposing Higher oxalate levels in HK - 2 cells lead to increased transcriptional activation of IL - 2R beta mRNA, which in turn boosts IL - 2R beta protein levels, which in turn induce modifications in the cell, including the generation of inflammation. Despite the fact that the specific mechanisms remain unclear, oxalate - induced activation may operate on cell membranes to initiate p38MAPK signalling.[55]

5.7 Kidney Stone Formation's Genetic Basis

Interactions between underlying genetic genes and environmental conditions may result in rare stone disorders. The appropriate function of renal epithelial cells is essential for the synthesis of promoters and inhibitors of crystallisation. The supersaturation of urine output is impacted by cellular failure, which releases ions such as citrate, oxalate, and calcium. Stones may develop due to certain genetic flaws.[56]

5.8 Kidney Stone Promoters and Inhibitors

Inhibitors are substances that slow down any process that is required to form stones, such as nucleation, supersaturation, crystal growth, and rate of aggregation. Urine often includes substances that inhibit the development of crystals.[57] However, not everyone responds to these inhibitors equally, which is why some people develop stones. However, if the crystals that develop don't become very big, they often leave the body unnoticed with a splash of urine after passing through the urinary system. Inhibitors might operate directly by interacting with crystals or indirectly by changing the urine's surrounding environment. Substances known as

inhibitors stop the nucleation, growth, aggregation, and crystal - cell adhesion when they adsorb onto the crystal's surface.[58]

Promoters, on the other hand, are chemicals that, via a variety of methods, aid in the production of stones. Cell membrane lipids, reduced urine volume, oxalate, calcium, sodium, cystine, and A few of the promoters include the elevation of calcitriol hormone via stimulation of parathyroid hormone. Recurrent stone formers were observed to excrete more oxalate in their urine while excreting less citrate.[59] Research findings suggest that oxalate may enhance the proximal tubule's ability to reabsorb water, salt, and chloride while also triggering kidney epithelium cells include several signalling pathways. Unbalanced levels of urinary stone promoters and inhibitors have often been associated with the formation of stones. Chemicals that are often thought to either encourage or impede the process of stone formation.[60]

6. Alternatives for Urolithiasis Prevention

Treating the underlying cause of stone development is essential for effective kidney stone prevention. Generally speaking, pharmaceutical usage and appropriate food management are necessary to stop kidney stone formation's first episodes as well as any subsequent ones.[61]

Regardless of the medicine used to treat their stone sickness or the underlying cause of their condition, It is important to advise patients to drink more water in order to maintain a minimum 2 - liter daily urine output. The simplest and most efficient way to change your lifestyle and Increasing your water or liquid intake may help avoid stone disease. Adequate consumption of euid lowers urine saturation and dilutes the factors that cause Crystallisation of CaOx. Consuming a diet low in oxalate more calcium via food are advised for absorptive hyperoxaluria.[62]

A high - salt diet raises the risk of stones by increasing urine calcium levels and reducing renal tubular calcium reabsorption. Because animal proteins include a high concentration of sulfur - containing amino acids, they also have a greater acid load, thus it's advisable to limit your consumption of them. Increased protein intake increases the excretion of calcium via bone reabsorption while lowering the pH and citrate levels in the urine. Consequently, you may need to eat fewer fish, pork, and poultry and stay away from foods containing vitamin D if your urine is very acidic. Rather, it is advised to consume more fruits and vegetables high in potassium.[63]

It used to be recommended that people who avoid dairy and other high - calcium meals in order to prevent the development of calcium stones.[64] It is not advisable to restrict calcium intake for those who are prone to kidney stones unless it is shown that they utilise the mineral excessively.[65] It's arguable, nevertheless, whether taking supplements of calcium is beneficial. Ascorbic acid is transformed in vivo into oxalate, which is why vitamin C has been connected to the formation of kidney stones. As a result, it is suggested to take supplements containing as little vitamin C as possible.[66]

7. Drug Therapy

7.1 Thiazide diuretics

RCTs have shown the efficacy of thiazide diuretics, such as hydrochlorothiazide, chlorthalidone, and indapamide, in lowering calciuria and the recurrence of stones. Additionally, these medications promote a positive calcium balance, which raises bone mineral density.6[7] Hypokalemia must be avoided since it may result in hypocitraturia, and sodium restriction must be used.12.5–25 mg of hydrochlorothiazide or chlorthalidone is often the beginning dosage. Potassium citrate supplements should be given to the majority of patients. Triamterene's limited solubility means that it should be avoided, however amiloride could assist prevent hypokalemia.[68]

7.2 Alkalinizing agents

Calcium crystal development and formation are inhibited by citrate. Its usage has been recommended for people who do not have this urinary anomaly but who have had calcium oxalate stones. It has also been recommended for patients with poor urine citrate excretion. It is recommended to use the potassium salt since supplementing with sodium citrate can cause increased calciuria.[69]

7.3 Allopurino

The sole known metabolic risk factor for hyperuricosuria is present in a small percentage of individuals with calcium oxalate stones. Crystals of calcium oxalate are easier to precipitate when uric acid is present. The effectiveness of allopurinol, 100 mg three times a day (we recommend 300 mg once a day), in preventing the development of calcium stones was shown in a single RCT.5. There is no evidence that allopurinol helps people with hypercalciuria.7[0]

7.4 Fish oil

Since the Inuit people of Greenland mostly eat fresh fish, kidney stones were almost nonexistent in this community, which sparked interest in fish oil supplements. Eicosapentaenoic acid supplementation lowers calciuria, yet this hasn't been verified in a randomised controlled trial.[71]

8. Conclusion

Globally, the prevalence of urolithiasis is rising, even in spite of notable progress in creating new medications to treat kidney stones. There is still much to learn about the development of renal stones. However, it is evident that the following factors—Randall's plaque, Kidney stone production is mostly influenced by renal cell injury, crystal retention, cell apoptosis, and related stone promoters or inhibitors. These seem to be significant objectives that result in the creation of a new plan to avoid kidney stone disease and medications that treat kidney stones. Better medication development will also be aided by the identification of novel targets for treatment based on cellular and molecular alterations associated with the development of stones. Moreover, a more thorough The discovery of drugs that dissolve stones will need a knowledge of the urolithiasis

pathways linked to inhibitors or promoters of stones. Additionally, via understanding the aetiology, pathophysiology, and genetic basis of kidney stone generation, new medications and approaches to the management of urolithiasis should be discovered soon.

References

[1] L. Giannossi and V. Summa, "A review of pathological biomineral analysis techniques and classiIcation schemes, " in An Introduction to the Study of Mineralogy, C. Aydinalp, Ed., InTechOpen, InTech, IMAA - CNR, Italy, 2012, http: //www.intechopen. com/books.

[2] M. Lopez and B. Hoppe, "History, epidemiology and regional diversities of urolithiasis, " Pediatric Nephrology, vol.25, no.1, pp.49–59, 2008.

[3] K. Mikawlrawng, S. Kumar, and R. Vandana, "Currentscenario of urolithiasis and the use of medicinal plants asantiurolithiatic agents in Manipur (North East India): a review, "International Journal of Herbal Medicine, vol.2, no.1, pp.1–12, 2014.

[4] S. R. Khan, M. S. Pearle, W. G. Robertson et al., "Kidneystones, " Nature Reviews Disease Primers, vol.2, p.16008, 2016.

[5] V. K. Sigurjonsdottir, H. L. Runolfsdottir, O. S. Indridasonet al., "Impact of nephrolithiasis on kidney function, " BMCNephrology, vol.16, no.1, p.149, 2015.

[6] Z. M. El - Zoghby, J. C. Lieske, R. N. Foley et al., "Urolithiasisand the risk of ESRD, " Clinical Journal of the AmericanSociety of Nephrology, vol.7, no.9, pp.1409–1415, 2012.

[7] A. D. Rule, V. L. Roger, L. J. Melton et al., "Kidney stonesassociate with increased risk for myocardial infarction, "Journal of the American Society of Nephrology, vol.21, no.10, pp.1641–1644, 2010.

[8] E. M. Worcester and F. L. Coe, "Nephrolithiasis, " PrimaryCare, vol.35, no.2, pp.369–391, 2008.

[9] E. N. Taylor, M. J. Stampfer, and G. C. Curhan, "Obesity, weight gain and the risk of kidney stones, " Journal of theAmerican Medical Association, vol.293, no.4, pp.455–462, 2005.

[10] M. Courbebaisse, C. Prot - Bertoye, J. Bertocchio et al., "Nephrolithiasis of adult: from mechanisms to preventivemedical treatment, " Revue MedicaleInternationale, vol.38, no.1, pp.44–52, 2017.

[11] S. B. N. Kumar, K. G. Kumar, V. Srinivasa, and S. Bilal, "Areview on urolithiasis, " International Journal of UniversalPharmacy and Life Sciences, vol.2, no.2, pp.269–280, 2012.

[12] J. M. Teichman and M. H. Joel, "Acute renal colic fromureteral calculus, " New England Journal of Medicine, vol.350, no.7, pp.684–693, 2004.

[13] T. Knoll, "Epidemiology, pathogenesis and pathophysiologyof urolithiasis, " European Urology Supplements, vol.9, no.12, pp.802–806, 2010.

[14] C. K. Chauhan, M. J. Joshi, and A. D. B. Vaidya, "Growthinhibition of struvite crystals in the presence of herbal extractCommiphorawightii, " Journal of Materials Science, vol.20, no.1, pp.85–92, 2008.

[15] O. W. Moe, "Kidney stones: pathophysiology and medicalmanagement, " <e Lancet, vol.367, no.9507, pp.333–344, 2006.

[16] V. Romero, H. Akpinar, and D. G. Assimos, "Kidney stones: a global picture of prevalence, incidence, and associated riskfactors, " Reviews in Urology, vol.12, no.2 - 3, pp. e86–e96, 2010.

[17] V. O. Edvardsson, O. S. Indridason, G. Haraldsson, O. Kjartansson, and R. Palsson, "Temporal trends in theincidence of kidney stone disease, " Kidney International, vol.83, no.1, pp.146–152, 2013.

[18] B. Afsar, M. C. Kiremit, A. A. Sag et al., ", e role of sodiumintake in nephrolithiasis: epidemiology, pathogenesis, andfuture directions, " European Journal of Internal Medicine, vol.35, pp.16–19, 2016.

[19] W. G. Robertson, P. J. Heyburn, M. Peacock, F. A. Hanes, and R. Swaminathan, "The e3ect of high animal proteinintake on the risk of calcium stone - formation in the urinarytract, " Clinical Science, vol.57, no.3, pp.285–288, 1979.

[20] K. B. Singh and S. Sailo, "Understanding epidemiology andetiologic factors of urolithiasis: an overview, " Scienti=c Visualization, vol.13, no.4, pp.169–174, 2013.

[21] N. H. SoIa and T. M. Walter, "Prevalence and risk factors ofkidney stone, " Global Journal For Research Analysis, vol.5, 2016.

[22] C. D. Scales, A. C. Smith, J. M. Hanley, and C. S. Saigal, "Prevalence of kidney stones in the United States, " EuropeanUrology, vol.62, no.1, pp.160–165, 2012.

[23] K. C. Joseph, B. Bharat, H. Parek, and M. J. Joshi, "Inhibitionof growth of urinary type calcium hydrogen phosphatedihydrate crystals by tartaric acid and tamarind, " CurrentScience, vol.88, pp.1232–1238, 2005.

[24] C. O'Callaghan, Edited by P. V. Yangkul and L. AmmiVisnaga, Eds., Blackwell Publishing Ltd., Oxford, UK, 2006.

[25] I. H. Zahid, A. S. Bawazir, and R. Naser, "Plant based nativetherapy for the treatment of Kidney stones in Aurangabad (M. S), " Journal of Pharmacognosy and Phytochemistry, vol.1, no.6, pp.189–193, 2013.

[26] A. P. Evan, "Physiopathology and Etiology of stone formationin the kidney and the urinary tract, " Pediatric Nephrology, vol.25, no.5, pp.831–841, 2010.

[27] N. Chhiber, M. Sharma, T. Kaur, and S. Singla, "Mineralizationin health and mechanism of kidney stone formation, "International Journal of Pharmaceutical Science Invention, vol.3, pp.25–31, 2014.

[28] C. Barbasa, A. Garciaa, L. Saavedraa, and M. Muros, "Urinaryanalysis of nephrolithiasis markers, " Journal of ChromatographyB, vol.781, no.1 - 2, pp.433–455, 2002.

[29] F. L. Coe, A. Evan, and E. Worcester, "Kidney stone disease, "Journal of Clinical Investigation, vol.115, no.10, pp.2598–2608, 2005.

[30] A. Chaudhary, S. K. Singla, and C. Tandon, "In vitro evaluationof Terminalia arjuna on calcium phosphate andcalcium oxalate crystallization, " Indian Journal of PharmaceuticalSciences, vol.72, no.3, pp.340–345, 2010.

[31] F. L. Coe, J. H. Parks, and J. R. Asplin, “, e pathogenesis andtreatment of kidney stones, ” New England Journal of Medicine, vol.327, no.16, pp.1141–1152, 1992.
[32] A. Skolarikos, M. Straub, T. Knoll et al., “Metabolic evaluationand recurrence prevention for urinary stone patients: EAU guidelines, ” European Urology, vol.67, no.4, pp.750–763, 2015.
[33] A. Bensatal and M. R. Ouahrani, “Inhibition of crystallizationof calcium oxalate by the extraction of Tamarix gallica L, ”Urological Research, vol.36, no.6, pp.283–287, 2008.
[34] D. R. Basavaraj, C. S. Biyani, A. J. Browning, andJ. J. Cartledge, “, e role of urinary kidney stone inhibitorsand promoters in the pathogenesis of calcium containingrenal stones, ” EAU - EBU Update Series, vol.5, no.3, pp.126–136, 2007.
[35] F. Dal - Moro, M. Mancini, I. M. Tavolini, V. De Marco, andP. Bassi, “Cellular and molecular gateways to urolithiasis: a new insight, ” Urologia Internationalis, vol.74, pp.193–197, 2005.
[36] D. V. Kishore, F. Moosavi, and D. R. K. Varma, “E3ect ofethanolic extract of Portulaca oleracea linn. on ethyleneglycol and ammonium chloride induced urolithiasis, ” InternationalJournal of Pharmacy and Pharmaceutical Sciences, vol.5, no.2, pp.134–140, 2013.
[37] D. P. GriQth, “Struvite stones, ” Kidney International, vol.13, no.5, pp.372–382, 1978.
[38] M. Dursun, A. Otunctemur, and E. Ozbek, “Kidney stonesand ceftriaxone, ” European Medical Journal of Urology, vol.3, no.1, pp.68–74, 2015.
[39] T. C. Ngo and D. G. Assimos, “Uric acid nephrolithiasis: recent progress and future directions, ” Reviews in Urology, vol.9, pp.17–27, 2007.
[40] K. Ahmed, P. Dasgupta, and M. S. Khan, “Cystine calculi: challenging group of stones, ” Postgraduate Medical Journal, vol.82, no.974, pp.799–801, 2006.
[41] K. P. Aggarwal, S. Narula, M. Kakkar, and C. Tandon, “Nephrolithiasis: molecular mechanism of renal stone formationand the critical role played by modulators, ” BioMedResearch International, vol.2013, Article ID 292953, 21 pages, 2013.
[42] S. R. Khan and D. J. Kok, “Modulators of urinary stoneformation, ” Frontiers in Bioscience, vol.9, no.1–3, pp.1450–1482, 2004.
[43] A. E. Krambeck, S. E. Handa, A. P. Evan, and J. E. Lingeman, “Brushite stone disease as a consequence of lithotripsy?, ”Urological Research, vol.38, no.4, pp.293–299, 2010.
[44] A. E. Krambeck, S. E. Handa, A. P. Evan, and J. E. Lingeman, “ProIle of the brushite stone former, ” Journal of Urology, vol.184, no.4, pp.1367–1371, 2010.
[45] M. Straub and R. E. Hautmann, “Developments in stoneprevention, ” Current Opinion in Urology, vol.15, no.2, pp.119–126, 2005.
[46] S. H. Obligado and D. S. Goldfarb, “, e association ofnephrolithiasis with hypertension and obesity: a review, ”American Journal of Hypertension, vol.21, no.3, pp.257–264, 2008.
[47] V. Butterweck and S. R. Khan, “Herbal medicines in themanagement of urolithiasis: alternative or complementary, ”Planta Medica, vol.75, no.10, pp.1095–1103, 2009.
[48] S. Joshi, B. T. Saylor, W. Wang, A. B. Peck, and S. R. Khan, “Apocynin treatment reverses hyperoxaluria inducedchanges in NADPH oxidase system expression in rat kidneys: a transcriptional study, ” PLoS One, vol.7, article e47738, 2012.
[49] I. P. Heilberg and N. Schor, “Renal stone disease: causes, evaluation and medical treatment, ” ArquivosBrasileiros deEndocrinologia&Metabologia, vol.50, no.4, pp.823–831, 2006.
[50] S. Kumar, D. Sigmon, T. Miller et al., “A new model ofnephrolithiasis involving tubular dysfunction injury, ” Journalof Urology, vol.146, no.5, pp.1384–1389, 1991.
[51] S. R. Khan, P. N. Shevock, and R. L. Hackett, “Acute hyperoxaluria, renal injury and calcium - oxalate urolithiasis, ” Journal of Urology, vol.147, no.1, pp.226–230, 1992.
[52] G. Gambaro, A. Fabris, D. Puliatta, and A. Lupo, “Lithiasis in cystic kidney disease and malformations of the urinary tract, ” Urological Research, vol.34, no.2, pp.102–107, 2006.
[53] K. Mikami, K. Akakura, K. Takei et al., “Association of absence of intestinal oxalate degrading bacteria with urinary calcium oxalate stone formation, ” International Journal of Urology, vol.10, no.6, pp.293–296, 2003.
[54] C. Kwak, H. K. Kim, E. C. Kim, M. S. Choi, and H. H. Kim, “Urinary oxalate levels and the enteric bacterium Oxalobacterformigenes in patients with calcium oxalate urolithiasis, ” European Urology, vol.44, no.4, pp.475–481, 2003.
[55] M. S. Parmar, “Kidney stones, ” British Medical Journal, vol.328, no.7453, pp.1420–1424, 2004.
[56] K. K. Malhotra, “Medical aspects of renal stones: review, ” Journal of Indian Academy of Clinical Medicine, vol.9, no.4, pp.282–286, 2008.
[57] D. J. Kok, S. E. Papapoulos, and O. L. Bijvoet, “Crystal agglomeration is a major element in calcium oxalate urinary stone formation, ” Kidney International, vol.37, no.1, pp.51–56, 1990.
[58] P. Cunningham, H. Noble, A. - K. Al - Modhefer, and I. Walsh, “Kidney stones: pathophysiology, diagnosis and management, ” British Journal of Nursing, vol.25, no.20, pp.1112–1116, 2016.
[59] S. Ahmed, M. M. Hasan, and Z. M. Alam, “In vitro urolithiasis models: an evaluation of prophylactic management against kidney stones, ” Journal of Pharmacognosy and Phytochemistry, vol.5, no.3, pp.28–35, 2016.
[60] E. O. Kajander and N. Ciftcioglu, “Nanobacteria: an alternative mechanism for pathogenic intra - and extracellular calciIcation and stone formation, ” Proceedings of the National Academy of Sciences, vol.95, pp.8274–8279, 1998.
[61] H. Xu, A. L. Zisman, F. L. Coe, and E. M. Worcester, “Kidney stones: an update on current pharmacological management and future directions, ” Expert Opinion on Pharmacotherapy, vol.14, no.4, pp.435–447, 2013.
[62] V. N. Ratkalkar and J. G. Kleinman, “Mechanisms of stone formation, ” Clinical Reviews in Bone and

Mineral Metabolism, vol.9, no.3 - 4, pp.187–197, 2011.

[63] S. R. Khan, F. Atmani, P. Glenton, Z. - C. Hou, D. R. Talham, and M. Khurshid, “Lipids and membranes in the organic matrix of urinary calciIc crystals and stones, ” Calci=ed Tissue International, vol.59, pp.357–365, 1996.

[64] M. S. Schepers, B. G. Vander, J. C. Romijn, F. H. Schr¨ooderand, and C. F. Verkoelen, “Urinary crystallizationinhibitors do not prevent crystal binding, ” Journalof Urology, vol.167, no.4, pp.1844–1847, 2002.

[65] S. R. Khan, “Renal tubular damage/dysfunction: key to theformation of kidney stones, ” Urological Research, vol.34, no.2, pp.86–91, 2006.

[66] M. Tsujihata, “Mechanism of calcium oxalate renal stoneformation and renal tubular cell injury, ” InternationalJournal of Urology, vol.15, no.2, pp.115–120, 2008.

[67] C. F. Verkoelen, B. G. vander Boom, and J. C. Romijn, “IdentiIcation of hyaluronan as a crystal - binding molecule atthe surface of migrating and proliferating MDCK cells, ”Kidney Inernational, vol.58, no.3, pp.1045–1054, 2000.

[68] M. T. Moryama, C. Domiki, K. Miyazawa, T. Tanaka, andK. Suzuki, “E3ects of oxalate exposure on Madin - Darby caninekidney cells in culture: renal prothrombin fragment - 1 mRNAexpression, ” Urological Research, vol.33, no.6, pp.470–475, 2005.

[69] S. R. Khan, P. A. Glenton, R. Backov, and D. R. Talham, “Presence of lipids in urine, crystals and stones: Implicationsfor the formation of kidney stones, ” Kidney International, vol.62, no.6, pp.2062–2072, 2002.

[70] M. E. Barros, N. Schor, and M. A. Biom, “E3ects of anaqueous extract from Phyllanthus niruri on calcium oxalatecrystallization, ” Urological Research, vol.30, pp.374–379, 2003.

[71] Y. I. Rabinovich, M. Esayanur, S. Daosukho, K. J. Byer, H. E. El - Shall, and S. R. Khan, “Adhesion force betweencalcium oxalate monohydrate crystal and kidney epithelialcells and possible relevance for kidney stone formation, ”Journal of Colloid and Interface Science, vol.300, no.1, pp.131–140, 2006.