International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Renal caliculi: Types, mechanism, therapeutic approaches encompassing role of GAGS, MGP, Hormones, UPTF1, CAI, Osteopontin

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International Journal of Science and Research Archive, 2024, 11(01), 2491–2501

Publication history: Received on 14 January 2024; revised on 21 February 2024; accepted on 24 February 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.11.1.0341

Abstract

Kidney stones are deposits in the renal pelvis, calyces, and ureters and reside in urine. Kidney stones undergo biomineralization pathogenesis via nucleation, aggregation, and growth of caliculi. The greater prevalence of kidney stones in men than in women may be due to the link between sex hormones. Kidney equilibrium is maintained with glycosaminoglycans inhibiting growth and aggregation. Sialylated glycoforms of urinary prothrombin fragment 1 prevent calcium stone development. Crystal adherence to tubules is inhibited by CAI, and osteopontin inhibits calculi formation. Medical treatments involve the use of alpha blocker, potassium citrate, thiazide, NSAIDS, opioids, antiemetics and other drugs used in treatment of kidney stone, Alpha adrenoceptor blockers, calcium channel blockers and corticosteroids help to expel renal stones, chemolytic treatment and it could be necessary to remove stones surgically if they are affecting kidney function with the use of techniques. Use of catheter, ultrasound, using a flexible scope equipped with a laser, HDAC inhibitors and many are recent advances in treatment lithiasis.

Keywords: Glycosaminoglycans; Maxtra Gla protein; Crystal adhesion inhibitor; UPTF1; Osteopontin

1. Introduction

Kidney lithiasis is characterised as the result of a variation in the regular crystallisation that occurs in urine in the urinary tract [1]. Kidney stones are solid particles formed by substances that reside in urine. The most prevalent signs include intense lower back pain, blood in the urine, vomiting and nausea, chills and a high temperature, and urine often odors foul or is hazy. Urine contains numerous wastes suspended in it [2].

Nephrolithiasis, often known as kidney stones, is the most frequent urinary system disorder, impacting around 12% of the global population and accounting for 600,000 cases in America each year. The condition is the consequence of a crystal or crystalline concretion passing from the kidney to the genitourinary system. Kidney stones are associated with a higher risk of chronic kidney disorders, end-stage renal failure, diabetes, cardiovascular disease, and high blood pressure [3]. Nephrolithiasis is extremely common in every demographic category in the Western world as well as elsewhere, and its incidence is increasing. Besides to the morbidity of the acute occurrence, stone disease frequently becomes a lifetime condition that requires preventative measures to reduce ongoing morbidity [4].

When crystals develop in a healthy person's urine during its stay in the urinary tract, they either don't form at all or are so tiny that they pass through the system without any problems (asymptomatic crystalluria). However, if the typical circumstances for urine crystallisation are changed, the rate of nucleation and development of the crystals may increase to the point where their size makes them difficult to remove [1]. Crystals occur when there is an excessive amount of waste in an inadequate amount of liquid. If the crystals aren't expelled from the human body with the urine, they will continue to take in additional substances and unite to create a larger solid. The kidneys, the body's chief chemist, typically remove these substances from the body through the urine. For most people, pee contains compounds that

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prevent stones from developing, or they are washed away by a sufficient amount of fluid. The mineral calcium, oxalate, urate, the amino acid cystine, xanthine, and phosphate are the substances that cause stones. Once produced, the stone may remain in the kidney or pass into the ureter through the urinary tract. Small stones can occasionally pass through the urinary system without causing any discomfort. However, immobile stones may result in a urine backup in the bladder, urethra, ureter, or kidney. This is the source of the discomfort [2].

Eighty percent of nephrolithiasis patients have calcium stones, the majority of which are mostly made of calcium phosphate or calcium oxalate. The other common kinds include cystine stones, the struvite (magnesium ammonium phosphate), and uric acid. It should be noted that a patient can have a stone with many crystal types in it. Nephrolithiasis affects around 12% of people globally and has rising prevalence and recurrence rates despite minimal effective treatment options. In the United States, the incidence is thought to be 600,000. Men are more likely than women to get kidney stones between the ages of 20 and 49 (2 to 1). Males have a greater lifetime recurrence rate than females. This fact is linked to the growing incidence of obesity brought on by unhealthy eating patterns and inactivity [5].

2. Mechanisms of stone formation

Kidney stone pathogenesis, also known as biomineralization, is a complicated biochemical process that is still poorly understood. Urine supersaturation and physicochemical alterations are two biological processes that lead to renal stone development [6]. The nucleation of the crystals that make up the stone, their growth or aggregation to a size where they can interact with an intrarenal structure, their retention inside the kidney or renal collecting system, and additional aggregation and perhaps secondary nucleation in order resulting in the clinical stone are the mechanisms involved in the formation of stones.

This series is viewed in. Crystals of stones either form in the kidney tubular fluid or the kidney interstitial fluid becomes supersaturated by their constituents. This supersaturation can be caused by decreased urine volume, altered urine pH, a greater elimination of stone element molecules, or an assortment of these factors. In comparison to typical healthy people, stone precursors' urine and, likely tube fluid, are frequently more strongly supersaturated, which promotes the nucleation and formation of crystals. The clinical stone is created by the long-term accumulation of extra components in both crystalline and organic matrix [7].

Nucleation, the process by which free ions combine to create tiny particles, is the first step in triggering the formation of kidney stones. Nucleation can happen on the surfaces of cells and the extracellular matrix as well as in the renal nephron. Following their formation, small crystals may go through secondary nucleation or aggregation, which are processes that transform the crystals that started out as single-component solutions into larger multi-component particles. Huge crystals may expand into enormous single crystals which adhere to particular intra-renal structures and continue to agglomerate, allowing the kidney to retain [8]

A solution is said to as supersaturated if it has more dissolved material in it than the solvent in it could normally dissolve. Supersaturation causes solutes to form precipitates in urine, which triggers nucleation and the formation of crystal concretions. In other words, crystallisation happens when two ions' concentration is greater compared to the saturation point in a solution. The pH and particular quantities of excess chemicals have an impact on the transition from a liquid to a solid phase. Risk factors for crystallisation include low urine volume and the amount of urinary saturation with regard to the components that form stones, such as calcium, phosphorus, uric acid, oxalate, and cystine. Therefore, both the kinetic and thermodynamic properties of a supersaturated fluid influence the crystallisation process. Therefore, avoiding supersaturation can help prevent lithiasis [6].

Kidney stone formation is known to be associated with low urine citrate excretion. By complexing with calcium in the urine, suppressing spontaneous nucleation, and halting crystal development and agglomeration, citrate prevents the formation of stones. A frequent metabolic disorder that affects 20% to 60% of stone formers is hypocitraturia [9]. ROS are thought to be an marker of oxidative stress. According to studies, ROS serve two purposes in ER stress signaling. NADPH oxidase (NOX), particularly is found in the ER, can promote the generation of ROS under ER stress. ROS can then control the UPR and restore ER homeostasis. However, ER oxidase 1 (ERO1) will partially promote a surge in ROS if the strong stimulus persists or is not eliminated in a timely manner, hence impairing the ability to reduce ER pressure. Overproduction of ROS within the ER causes calcium to be accumulated in the mitochondria, which worsens the damage done to the mitochondria. Inhibiting SOD will cause ROS to accumulate more, which will worsen ER stress and encourage the development of kidney stones. Previous research has shown that SOD can reduce the stress caused by ROS [10]. According to Sakee et al., there are several different and intricate pathophysiological processes that lead to the production of calcium kidney stones. These mechanisms include minimal urine volume, elevated calcium levels, hyperuricosuria, hypocitraturia, hyperoxaluria, and alterations in urine pH [11].

3. Types of urinary calculi

The primary constituents of the stone matrix comprise 2-3% of their overall dry weight and are mostly macromolecules that are often found in urine. 64% of them are protein, 9.6% are non-amino carbohydrates, 5% are hexosamine as glucosamine, 10% are bound water, and the remaining portion is inorganic ash, according to Boyce. Lipids have additionally been shown to serve as important components of the stone matrix, although not being found by Boyce. Urinary calculi come in four varieties: mixed calcium stones (Struvite), uric acid stones, cystine calculus, and certain rare varieties.

3.1. Calcium stones

About 75% of all calculi in the urinary tract are calcium stones, which are the most prevalent kind. These stones might be composed entirely of calcium phosphate (5%) or pure calcium oxalate (50%) or a combination of the two (45%).

- **Origin:** The cause of calcium stones varies. It is estimated that idiopathic elevated calcium levels without hypercalcaemia affects 50% of individuals with calcium stones. Hyperparathyroidism or a malfunction in the kidney or colon are the most prevalent causes of hypercalcaemia and hypercalciuria, which affect around 10% of cases. Nearly 15% of individuals with calcium stones also have hyperuricosuria, although without any abnormalities in calcium metabolism or blood uric acid levels. About 25% of people with calcium stones have no recognised aetiology since their urine output is normal. It is characterised as "idiopathic calcium stone disease" and affects around 25% of individuals with calcium stones; the aetiology is unclear because there is no abnormalities in the expulsion of calcium, uric acid, or oxalate in the urine.
- **Pathogenesis:** An imbalance between the concentration of inhibitors in the urine and the amount of super-saturation of the ions producing the stones accounts for the process of calcium stone development. The most likely location where calcium phosphate and/or calcium oxalate crystals form in the tubular lining, or around a piece of debris functioning as a stone nidus in that tubule. As more and more crystals are deposited around the nidus, the stone progress. Other predisposing variables that enhance the risk of calcium stone formation include alkaline urine pH, reduced urine volume, and increased excretion of uric acid and oxalate.
- **Morphology**: The typical calcium stone is ovoid, hard, and has a rough, granular surface. It typically measures less than a millimetre. Due to ancient blood pigment accumulated in them from frequent damage to the urinary system from these sharp-edged stones, their surface can become dark brown.

3.2. Mixed (struvite) stones

Mixed calculi are additionally referred to as "Struvite stones" or "triple phosphate stones" because struvite, a mixture of the mineral magnesium, ammonium, and calcium phosphate, makes up around 15% of urinary calculi.

- **Etiopathogenesis**: Urinary tract infections by urea-splitting microorganisms that generate urease, such as Proteus species and, less frequently, Pseudomonas, Klebsiella, and Enterobacter, lead to the formation of struvite stones. For this reason, they are sometimes called infection-induced stones. E. Coli does not, however, make urease.

Struvite stones possess a yellow-white or grey morphology**.** They often have an uneven form and are soft and friable. Struvite stone is characterised by massive, solitary stones that commonly occur in the renal pelvis. One such stone is called a "staghorn stone."

3.3. Uric acid stones

Uric acid calculi, which make up about 6% of urinary calculi, exist radiolucent in contrast to radio-opaque calcium calculi. The etiology of uric acid stones is often associated with hyperuricemia alongside hyperuricosuria, such as primary gout and secondary gout caused by myeloproliferative disorders (e.g., in leukemias), especially in patients undergoing chemotherapy and receiving uricosuric drugs (e.g., salicylates, probenecid). Other factors that can contribute to the formation of uric acid stones include low urinary volume and acidic urine pH (below 6).

- Pathogenesis: Uric acid is soluble at pH 7 (200 mg/dL) and pH 5 (15 mg/dL). As a result, as urine acidity rises, uric acid solubility falls and uric acid crystal precipitation rises, which promotes the development of uric acid stones. The most common cause of uric acid calculi is hyperuricosuria, but hyperuricaemia is present in around 50% of cases.

Uric acid stones have a smooth, firm, yellowish-brown morphology and are frequently numerous.

3.4. Cystine stones

Cystine stones: 2% or fewer of urinary calculi are composed of cystine stones.

The etiology of cystine stones and cystinuria is attributed to a commonly identified impairment in the transportation of cystine and amino acids via the renal tubules' cell membranes and the mucosa of the small intestine.

Pathogenesis: The least soluble of the naturally existing amino acids, cysteine, is excreted excessively as a result, which causes crystals to develop (cysteine calculi).

Morphology: These are tiny, spherical, smooth, wavy, yellowish, and frequently numerous.

3.5. Other calculi

A mere two percent of urinary calculi are made up of other uncommon forms, such as those resulting from genetic abnormalities in the metabolism of enzymes, such as xanthinuria, which can cause xanthine stones [12].

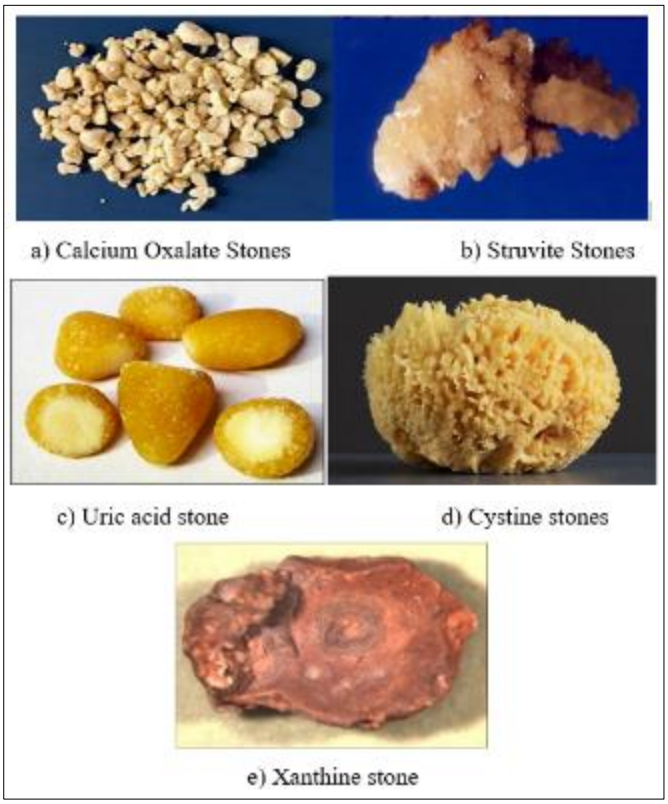

Figure 1 Types of urinary calculi

4. Role of sex hormones, glycosaminoglycan, matrix gla protein, crystal adhesion inhibitor and osteoponin in calcium oxalate nephrolithiasis

4.1. Androgens and Estrogens

According to statistical assessments, the prevalence of Calcium oxalate nephrolithiasis is 2-3:1 greater in males than in females. The exact procedure is yet unknown, though. According to earlier research, oestrogens reduce kidney calcium oxalate crystal formation, plasma oxalate concentration, and urine oxalate excretion. Conversely, androgens raise these parameters. Furthermore, the link between kidney stone production and sex may be due to increased androgen signaling. In order to enhance oxalate production and eventually cause kidney stones, androgen receptor (AR) signaling can directly upregulate hepatic glycolate oxidase and kidney epithelium nicotinamide adenine dinucleotide phosphate oxidase (NAPDH), subunit p22-PHOX, at the transcriptional level. According to Peng and colleagues, testosterone has a role in the development of nephrolithiasis by inducing necrosis and apoptosis in epithelial cells of the kidney via the HIF-1α/BNIP3 pathway. Changtong et al. found that testosterone may exacerbate kidney stone illness by increasing

surface α-enolase, which in turn enhances COM crystal-cell adhesion. Zhu et al. showed that AR may lower COM crystal phagocytic activity of macrophages and prevent macrophage recruitment by downregulating miR-185-5p, which in turn reduces colony-stimulating factor 1 (CSF-1) signals. These results imply that androgen receptor signaling could have a major role in the pathogenesis of nephrolithiasis [13].

4.2. Glycosaminoglycan role on kidney

GAGs (glycosaminoglycan) are crucial for maintaining the kidney's equilibrium. The primary location of glycosaminoglycan metabolism and excretion is the kidney. They cause the Glomerular Basement Membrane (GBM) to become negatively charged, which is crucial for the development of nephritic illnesses as well as the regular function of GFB [14]. Heparin and chondroitin sulphate are two examples of glycosaminoglycans that prevent calcium oxalate crystals from growing and aggregating [15]. Urinary GAG along with additional macromolecules have an inhibitory action that prevents renal cell damage and stone formation. Stone formers frequently exhibit deficiencies in the excretion of GAG in the urine, suggesting that GAG may play a more significant part in lithogenesis than earlier recognized. Thus, in some high-risk individuals, GAG supplementation may be helpful in preventing the development of stones, and aberrant urinary GAG excretion may be inherited in family members of kidney stone disease patients. It seems that the stone-inhibiting effect of CS reduced the development or production of calcium oxalate crystals [16]. The specific kind of glycosaminoglycan present and its intrinsic acidic qualities may ultimately determine its function as urine inhibitors of stone formation [17].

4.3. UPTF1 role on renal cell

Calcium oxalate crystals bind to kidney cell surfaces, which is now widely accepted as a probable cause of caliculi formation, as well as nephron blockage by Calcium oxalate crystal aggregates. Sialylated glycoforms of urinary prothrombin fragment 1 may prevent the development of calcium oxalate stones by encompassing the crystals' surface. This indicates that urinary prothrombin fragment 1 performs the functions that have been identified, which include lowering the possibility of crystal aggregation and preventing crystal–cell adhesion by hiding the contact between the calcium ions on the crystal surface and the kidney cell surface throughout the nephron. The primary rationale for the impediment of Calcium oxalate mineral aggregation and the prevention of Calcium oxalate crystal adherence to renal cells is the glycosylation of UPTF1 [18]. in urinary PTF1's glycosylation in individuals who produce stones are thought to affect the protein's ability to fend against calcium urolithiasis [18].

4.4. Matrix Gla protein

Vascular smooth muscle cells (VSMCs) & chondrocytes both have high levels of expression for matrix Gla protein (MGP), a vitamin K-dependent protein that is synthesized in bone and various other mesenchymal cells [19]. Patients with chronic kidney disease (CKD) are incredibly vulnerable to vascular disease. One prevalent risk factor for chronic kidney disease (CKD) is vascular calcification (VC), which can appear as both medial & intimal mineralization with different pathologies. Furthermore, CKD is commonly accompanied with vitamin K insufficiency, which is linked to elevated plasma levels of dephosphorylated uncarboxylated MGP (dp-ucMGP) [20]. Vascular calcifications are linked to elevated levels of dpucMGsP, MGP has been shown to block calcification. It may be possible for MGP to hinder crystallisation in the kidney, where it is expressed. In vitro, MGP expression was elevated in NRK-52E tubular cells and in rat kidneys upon exposure to calcium oxalate crystals (*in vivo*) (21). Vascular calcification is a dynamic process involving proteins and molecules rather than a passive, degenerative, incurable illness. The strongest natural calcification inhibitor in the human body, MGP is closely linked to coronary artery disease, mortality, and all forms of calcification. Supplementing with vitamin K exogenously could enhance its function, minimize calcification, and offer defence against cardiovascular disease and death (22).

4.5. Crystal adhesion inhibitor (CAI)

Using gel filtration chromatography, a 39-kDa glycoprotein known to be constitutively released by cells in the kidney was purified. It is unique and structurally unrelated to recognised inhibitors of the calcium oxalate crystallisation, according to amino acid microsequencing. Thus, crystal adhesion inhibitor, or CAI, was the term given to it. Several rat tissues, including the kidney, heart, pancreas, liver, and testis, were shown to have immunoreactive CAI. The presence of CAI on the membrane of plasma and in the cytoplasm of renal cells was shown by immunohistochemistry. Crucially, CAI can be isolated from normal human urine by employing the technique of calcium oxalate monohydrate crystal affinity chromatography. In vivo, CAI may provide a crucial line of defence against the crystals adhering to tubular cells and causing renal stones.

4.6. Osteopontin (OPN)

An important element of the mineralized extracellular matrices that surround bones and teeth is the highly phosphorylated sialoprotein known as osteopontin [23]. This glycoprotein is pleiotropic, implying that it is expressed in multiple cell types in both humans and animals, such as immunological, bone, smooth muscle, along with epithelial and endothelial cells. OPN additionally exists in urine and the kidneys, namely in the distal nephrons and the thick ascending limbs of the loop of Henle [24]. OPN is closely associated with immune cell infiltration. For example, OPN is a pro-inflammatory factor that may activate macrophages (which differentiate into M1 macrophages), T cells (which differentiate into T1 cells), mast cells (which breakdown to expel various inflammatory mediators), and other inflammatory cells that contribute to kidney failure and the development of stones. Renal fibrosis results from the infiltration of monocyte macrophages into the kidneys caused by large-scale OPN production from damaged kidney cells. This process leads to the differentiation of monocytes into the M1 pro-inflammatory phenotype. Currently, the primary oral medication for minimizing stones is citrate, which the guideline suggests as a litholytic medication [25]. In animal models, the production of osteopontin and the development of urinary stones have been significantly reduced by osteopontin antibodies and cyclosporine A, which inhibits the release of mPTP [26].

5. Treatment of renal stones

5.1. Drugs used in treatment of renal stones

- **Alpha Blockers** By reducing spasms in these tubes, alpha blockers aid in the relaxation of the ureter's muscles, which transport urine from the renal system to the bladder. This can assist in reducing any discomfort felt during the passing of a kidney stone. Additionally, when using this drug, larger small crystals can migrate more quickly—taking a few days instead of several weeks [27]. Benign prostatic hyperplasia, or an enlarged prostate, is treated with alpha blockers. Kidney stone therapy has not received approval for using them. Specifically, off-label usage of tamsulosin, an alpha blocker, occurs sometimes
    - About 50 among the 100 persons noticed the stones flush away in four weeks without the use of alpha blockers.
    - In approximately 73 among the 100 cases, the stones disappeared after four weeks when using alpha blockers [28].
- Potassium citrate inhibits the growth and recurrence of kidney stones. Kidney stones caused by uric acid can also be avoided and dissolved with the use of potassium citrate.
- **Thiazide Diuretics**: The quantity of calcium discharged into the urine can be decreased by thiazides. These include indapamide, hydrochlorothiazide, and chlorthalidone; they all aid in preventing the recurrence of kidney stones, particularly in those with elevated urine calcium levels.
- Kidney stones can be avoided with allopurinol by reducing the body's production of uric acid. Those who consume a lot of animal protein in their diet or who have gout may find this drug very helpful [27,29]

5.2. Drugs that relieve the symptoms such as Pain and Vomiting or Nausea Caused by Kidney Stones

- **Analgesics or Painkillers:** These are among the most widely prescribed drugs for kidney stone pain and inflammation relief. A narcotic or a nonsteroidal anti-inflammatory drug can be an analgesic. Acetaminophen, Butorphanol, Meperidine, Nalbuphine, Ketorolac, Ibuprofen, Meloxicam, and Oxycodone are among the medications in this class [30]
- **NSAIDs (non-steroidal anti-inflammatory drugs):** Nonsteroidal anti-inflammatory drugs should be the preferred analgesic option for patients presenting to the emergency department with renal colic. A-blockers could be of patient benefit when used for distal ureteral stones more than 5 mm in size [31]. When patients with renal colic come to the emergency room, nonsteroidal anti-inflammatory medications (NSAIDs) should be the first choice for analgesics. A-blockers may be beneficial to patients if they are administered for distal ureteral stones larger than 5 mm. They produce immediate relaxation of the ureter's muscles. They minimise the swelling and inflammation brought on by the stone in the ureters. They decrease the production of urine, which lessens pressure exerted by the stone from above.
- **Acetaminophen:** In addition, mild-to-moderate renal colic—abdominal discomfort brought on by kidney stones—can be treated with paracetamol. Although it doesn't reduce inflammation, it has the benefit of being safe to take while pregnant.
- The oral drugs take a while to start working, and patients experiencing renal colic might vomit up while taking the medication. Injectable or rectal administration of the medications are also possible. These medications might cause bleeding from the digestive tract and discomfort in the stomach. They increase the risk of acute

renal failure because they lower urine filtration, particularly in individuals with cirrhosis, dehydration, kidney disease, or other kidney-damaging medications.

- **Opioids**: Narcotic medicines such as tramadol and morphine, as well as opioids, help alleviate pain. In spite of their rapid alleviation, they have side effects that include drowsiness, nausea, respiratory depression, and misuse potential. As such, medical practitioners should utilise them with caution.
- **Antiemetics**: Metoclopramide, for example, could be utilised to alleviate nausea and vomiting if required, particularly when used with opioids. As soon as the discomfort is reduced in the majority of patients, however, it subsides vomiting.

5.3. Drugs that help to expel kidney stone

Smaller stones frequently expel themselves on their own, especially those that are lower in the urinary system and have a diameter of less than 10 mm. A collection of drugs known as medical expulsive treatment (MET) aid in the stone's removal. These might include an NSAID, an antiemetic, an opioid painkiller when necessary for brief periods of time (5 to 10 days), an alpha blocker such as terazosin as well as a drug that blocks calcium channels like nifedipine, a corticosteroid medication like prednisone, and/or an NSAID.

- Alpha adrenoceptor blockers: Tamsulosin and terazosin, two examples of alpha adrenoceptor blockers, relax and alleviate lower urinary tract muscular spasms. They lessen discomfort and aid in the stone's removal.
- Calcium channel blockers: A calcium channel blocker used to treat cardiovascular diseases including angina and hypertension is nifedipine. It helps the stone pass through the urinary system by relaxing its smooth muscles. It can be used alone or in conjunction with tamsulosin and terazosin.
- Corticosteroids: Strong anti-inflammatory medications such as prednisone can lessen inflammation brought on by kidney stones. They should be taken cautiously though, as they do have adverse effects, particularly when used over extended periods of time [32]

5.4. Others

- Renal stone development is a global issue that affects all ethnic, cultural, and geographic groups equally. It is possible to avoid recurrent pebble formation by following sensible dietary and hydration guidelines and by using targeted pharmaceutical intervention. Many herbal remedies are widely used to stop the production of recurrent stones. Researchers are now concentrating on oxalate-degrading bacteria to control kidney stones [33].
- The cornerstones of therapy for the majority of caliculi are focused dietary adjustments and improved hydration consumption. A sufficient calcium intake and limits on sodium, protein, and oxalate intake are among the specific dietary treatments linked to a lower risk of developing calcium stones. If lifestyle modifications are unable to reduce the chance of a stone recurrence, medical intervention may be necessary. This medication must be customised to address the particular metabolic anomalies that indicate a patient's risk of recurrence. Citrate salts, thiazides, and uric acid-lowering medications are among medical choices for idiopathic the mineral calcium stone illness. The preferred course of treatment for uric acid stone illness is also alkali salts. Although acetohydroxamic acid is a tried-and-true second line treatment, surgery is still the primary method of managing struvite stone disease. Changes in lifestyle are necessary for cystinuria and may need thiol-binding agents [4].
- It was suggested that magnesium may be utilised to avoid kidney stones in the 1920s when it was discovered to have the ability capable in enhancing the solubility of the mineral calcium oxalate in vitro. Rats on a low-magnesium diet quickly developed renal stones. In the proximal tubules, precipitation took place, especially of the calcium phosphate (hydroxyapatite) crystals. This might be accomplished as well through supplying rats a diet low in vitamin B6, however the development of stones was avoided if the diet comprised of magnesium supplements [34] [35].
- The functions of three novel medications in the targeted therapy of kidney stones are highlighted. A nonabsorbable ion-exchange resin called cellulose sodium phosphate (Calcibind) has a restricted range of applications in the management of calcium stones related to absorptive hypercalciuria Type I. Patients with persistent urea-splitting UTIs with struvite stones could benefit from acetohydroxamic acid (Lithostat), a urease inhibitor, as an adjuvant medication. Patients with hypocitraturic calcium phosphate and calcium oxalate stones can benefit clinically from potassium citrate (Urocit), an experimental medication. Patients with uric acid stones can also benefit from the alkalinizing drug potassium citrate [35]

5.5. Drugs used to Dissolve the Kidney Stones / Chemolytic Treatment

The delivery of certain fluids into the urinary system in order to dissolve the stones is known as chemolytic therapy. The solution is administered orally or locally by percutaneous injection (via a nephrostomy tube). To make sure that

excessive pressure doesn't accumulate in the kidney, the patient should have either two nephrostomy tubes or one nephrostomy tube with a ureteric stent if the medication is administered locally. These days, local irrigation is seldom taken out. Oral potassium citrate aids in the dissolution of tiny stone fragments and guards against future stone formation following short wave lithotripsy or percutaneous nephrolithotomy.

5.6. Kidney stone surgery

Surgical removal of kidney stones that are too big to pass naturally, too painful, or infected is known as **kidney stone surgery.** It can also be necessary to remove stones surgically if they are affecting kidney function. A kidney stone is either surgically removed whole or in fragments, or it is simply blasted apart so that the body can eliminate it. The size, location, and preference of the patient are among the factors that influence the sort of surgery that is performed.

- The least intrusive technique for removing stones is shock wave lithotripsy (SWL), which is the first line of treatment for the majority of kidney stones and many ureteral stones. In this operation, a kidney stone is broken up into little, fine fragments utilising high-energy shock waves. By doing this, the fragments might leave the body and travel easily via the urinary tract.
- **Ureteroscopy**: For the treatment of stones in the ureter, specifically those nearest to the bladder, ureteroscopies (URS) are performed. The stone is located by passing a tiny, flexible tube termed a ureteroscope up the ureter and through the bladder and urethra. The stone is taken out in its entirety or, if it's too big, is first broken up using a laser.
- **Percutaneous nephrolithotomy, or PNL**: The procedure known as percutaneous nephrolithotomy, or PNL, is typically performed on patients with large stones (those measuring more than 20 mm) or staghorn stones, which are big, branching stones linked to tract infections. In order to observe and eliminate the kidney stone, a tiny incision in the back is used to introduce an endoscope during this procedure. Before the stone gets eliminated, it could be blasted up into smaller components using a laser. In some cases, a nephrostomy tube may be temporarily inserted through the skin into your kidney to help drain urine.
- **Laparoscopic and Robot-Assisted Surgery**: Compared to the operations previously discussed, laparoscopic and robot-assisted surgery involves greater invasiveness. It is frequently utilised in a situation that one among them fails. The medical professional makes tiny incisions in the patient's abdomen and uses thin surgical equipment to remove the stone. In the event that a robot is utilised, the surgeon operates robotic hands that are fitted with surgical equipment.
- **Open Surgery**: There are very few cases of open surgery. It can be applied to individuals with staghorn stones, intricate kidney or ureter anatomy, severe obesity, or for whom minimally invasive methods have not been successful. An incision is created in the patient's back or belly to remove the stone during open surgery. To temporarily drain pee, a nephrostomy tube is implanted [36].

6. Recent drug therapy in management of kidney stone

- When a stone moves through the ureter, muscle relaxants assist in reducing the contractions causing discomfort. Scientists at Massachusetts General Hospital and MIT are currently developing a potential treatment that could accelerate up kidney stone passage and reduce the discomfort. Researchers have discovered a combination of two medications that could be administered directly into the ureter using a device resembling a catheter and that relax the walls of the tube that joins the kidneys and bladder [37]
- Patients with minimum discomfort, no surgery, and no anaesthesia can now be treated for kidney stones with a novel technique that employs ultrasound to realign and break up renal calculi. The National Kidney Foundation reports that kidney stones cause more than 500,000 visits to emergency departments annually. According to the organisation, around 10% of people will get a stone at some time in their lifespan. Nineteen patients had their stones moved, two of whom had the stones depart from the ureter into the bladder as a result of the procedure. Once the stone was removed from the ureter, one patient experienced immediate comfort [38].
- Urologists at UCI Health have tested a novel laser technique that may reduce kidney stones of any size to a dust which can be removed from the body by flushing or suctioning. During lithotripsy, without any incisions, lasers have been utilised to break up the stones. Using a flexible scope equipped with a laser, the urologist examines and breaks up the stone. The laser fibres are as tiny as three human hairs. Most urologists nowadays utilise holmium lasers to break kidney stones, however the thulium fibre laser can shatter stones in the kidneys into pieces that have dimensions typically 10 times smaller. The thulium laser produces smaller particles that are simpler to remove from the kidney by flushing or suction [39].
- The scientists at Washington University School of Medicine in St. Louis claim that a new mouse study suggests a class of medications authorised to treat epilepsy and leukaemia may also be beneficial against kidney calculi.

Histone deacetylase inhibitors, or HDAC inhibitors for short, are the medications. Two of them, trichostatin A and vorinostat, were discovered by the researchers to reduce the amounts of magnesium and calcium in the urine. Kidney stones are mostly composed of calcium and magnesium. When the function of a gene known as claudin-14 is reduced, the kidney's natural filtration mechanism works as intended. However, calcium and magnesium are prevented from re-entering the circulation when the gene is active. Instead of directly affecting claudin-14, vorinostat and trichostatin A imitate these so-called micro-RNA molecules, therefore regulating the gene's activity. The medications' ability to alter microRNA activity makes them appealing as possible kidney stone therapies [40].

7. Conclusion

The present reassessment conveys entropy about the renal lithiasis etiology, types of caliculi like calcium oxalate, uric acid, struvite, and cystine and various treatment procedures for pain, to dissolve or expel renal stones. Numerous surgery techniques are also available to eliminate kidney stone via a procedure called shockwave lithotripsy, uteroscopy, laparoscopic nephrolithomy, or nephrolithotripsy. Glycosaminoglycans, UPTF 1, Crystal adhesion inhibitor, estrogens prevent growth & aggregation preventing calcium stone formation. Kidney stones are associated with a higher risk of chronic kidney disorders, end-stage renal failure, diabetes, cardiovascular disease, and high blood pressure. The scientists across the globe working to advance the therapy of renal caliculi

Compliance with ethical standards

Acknowledgments

The authors are grateful to the principal (Prof. M. Ganga Raju) and management of the Gokaraju Rangaraju College of pharmacy, for the constant support and encouragement during the course of the work.

Disclosure of conflict of interest

All authors have no conflicts of interest to declare.

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