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From Calculi to Infection: A Comprehensive Review of the Dual Burden of Kidney Stones and UTIs

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ABSTRACT:
Infection in the urinary tract and stones in the kidney are common, frequently linked illnesses that have a big impact on public health. With an emphasis on the cyclical relationship between recurring infections and stone development, this review offers a thorough examination of the pharmacological and clinical aspects of the relation between kidney stones and UTIs. The composition of kidney stones, such as calcium oxalate, uric acid, and struvite, is categorized in the article. Special attention is paid to infection-related stones, such as struvite, which are directly linked to chronic.UTIs caused by urease-producing bacteria, such as Klebsiellapneumoniae and Proteus mirabilis.We examine factors that increase risk such as urinary stasis, metabolic diseases, dehydration, anatomical anomalies, and recurrent catheterization that are linked to both UTIs and stone formation.The pathophysiological processes are thoroughly investigated, with special attention paid to how urease activity and bacterial biofilms contribute to urine's alkalinization, which causes crystallization and the formation of stones.Pharmacological treatments including antibiotics, urease inhibiting agents, and citrate therapy are highlighted in the discussion of treatment choices, along with surgical possibilities like lithotripsy and percutaneous nephrolithotomy. Preventive actions aimed at reducing infection and stone.This review emphasizes how crucial it is to diagnose and treat individuals with recurring kidney stones and UTIs using an integrated, multidisciplinary strategy. Preventing the infection-stone cycle and enhancing patient outcomes require early discovery, precise classification, and specialized pharmaceutical therapy.

KEYWORDS: kidney stone , categories , relation between uti and kidney stone , pathophysiology , diagnosis , treatment

I. INTRODUCTION:

In the Western world, 5% of women and 12% of men suffer from kidney stone disease[1] .Furthermore, it is a significant contributor to urinary tract morbidity [1,31]. . The upper and lower urinary tracts are the two primary sections of the urinary system. The kidney and ureters comprise the upper urinary tract, whilst the bladder and urethra comprise the lower tract [32]. A chemical imbalance in the urine causes stone formation, which can happen anywhere in the urinary system . When crystal-forming chemicals including calcium, phosphorus, and urate supersaturate the urine, the process is likely to occur [2] . Low levels of inhibitory substances, including citrates, can raise the risk. After that, precipitated crystals may combine to form stone, which could eventually become big enough to impede [3]

A major contributor to the risk for bladder infections is chronic renal stone disease. When the two conditions coexist, pyelonephritis may develop, which can result in a progressive decline in renal function and, in rare cases, end-stage kidney disease(33) . If therapy is not received, pyelonephritis may sometimes worsen and progress into either the potentially fatal emphysematous pyelonephritis (EPN) or the uncommon xanthogranulomatous pyelonephritis (XGP)[34] . Furthermore, the persistence of kidney stones can cause local inflammation. and irritative alterations that can lead to epithelial dedifferentiation and dysplasia, which can favour the development of cancer and increase its likelihood by more than double. [4,35]

Severe, irritable discomfort that radiates to the groin is the typical symptom of a ureteric colic. The discomfort is usually referred to as the worst ache that the individual has ever experienced. Whenever calculi block the urinary system, ureteric colic develops. This condition affects the narrowest regions of the ureter, including the vesicoureteric junction (VUJ), the pelviureteric junction (PUJ), and the area surrounding the pelvic brim where the

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iliac vessels enter.Although it may be connected, the position of pain may not accurately indicate where the stone would be located in the urinary system. The stone may cause symptoms of bladder irritation when it gets closer to the vesicoureteric junction. [5]
Based on clinical and laboratory features, pyelonephritis is typically easy to diagnose.

As a catalyst for crystallization, increased urine supersaturation causes the formation of crystalline particles, which causes supersaturation and the buildup of kidney stones . [6] [36] . Failure of crystallization inhibitors results in nephrolithiasis. Compared to pure solvents, inhibitors enable higher levels of salts of calcium in solution. Calcium salts are hence metastable in urine. In actuality, stone cohorts produce more saturated urine than components without stones[37]. Figure -01 represents the introduction to the kidney stone and which causes urinary tract infection.

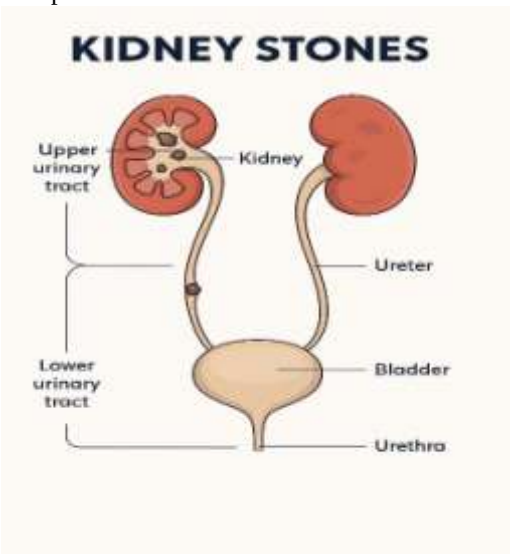

Fig 1: Introduction of kidney stone which causes urinary tract infection

II.CATEGORIES AND RISK FACTORS :

According to their mineralogical makeup, kidney stones can be classified into five primary types: calcium oxalate (CaOx; 65.9%), carbapatite (15.6%), urate (12.4%), struvite [or magnesium ammonium phosphate], 2.7%, and brushite (1.7%). [7]

Calcium-based stones

Kidney stones are often categorised as Kidney Stone according to their primary crystalline makeup . Calcium is the most prevalent inorganic component among all kidney stones, according to numerous research conducted in various locations[38,39]The most common component of calcium stone is calcium oxalate (CaOx), either alone or in combination with other substances such calcium phosphate (CaP) . Depending on how hydrated it is, CaOx can take on three different crystalline forms. These consist of CaOxtrihydrate, CaOxdihydrate (COD; CaC2O4·2H2O), and CaOx monohydrate (COM; CaC2O4·H2O) . [8]

Uric acid stones:

The formation of uric acid stones is favored by high concentrations of uric acid in the urine, especially when the urine is acidic [40]. As urine pH decreases, uric acid solubility declines sharply from 200 mg/dL at pH 7 to just 15 mg/dL at pH 5 [9].

Phosphate-calcium stones:

About 10–20% of all kidney stones are calcium phosphate stones, a kind of urolithiasis stone], which is a major urological issue worldwide. Recent studies have shown that renal phosphate absorption and associated phosphaturia are frequently the cause of calcium urolithiasis. People who have hyperphosphaturia, or extremely high phosphate levels in their urine, are more likely to experience these stones again [19]

Magnesium ammonium phosphate, or struvite stones:

Magnesium ammonium phosphate or struvite stones are two types of urinary tract stones

International Journal of Pharmaceutical Research and Applications
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that can form. People who have infections in the urinary tract due to bacteria produced by urease enzymes , like Klebsiellaetc, are more likely to develop these stones(15) . This kind of urinary stone makes up about 10–15% of all instances, despite being less frequent than CaOx stones. Both women and those with previous incidents of recurrent UTIs are more likely to have them(41 ,43) . When bacteria-produced urease breaks down urea in the urine, the pH rises and struvite crystals that can combine and form stones are formed(42). Struvite stones are made of ammonium, magnesium, and phosphate. [20]

Protease-related stones:

HIV-positive patients on the inhibitor of protease indinavir sulphate medication are more likely to develop protease-related stones. In 4-12% of patients receiving therapy, the usage of this medication may result in the development of such stones.(23)

III.SYMPTOMS:

Kidney stones, renal calculi, nephrolithiasis, or urolithiasis are hard, crystalline masses that can accumulate in your kidneys. Depending on what caused the disease, these stones can be of various sorts. Your risk of developing them may be increased by dehydration, poor eating habits, obesity, digestive disorders, and specific procedures, drugs, and supplements. Any or all of the following symptoms are likely to occur if you have them:

Sharp pains beneath your ribs in your back and side - The kidney may enlarge (hydronephrosis) as a result of the stone's passage through the small ureter, blocking urine flow and setting off pain receptors in that area.

Radiating discomfort in your groin and lower abdomen - The ureter is a small, muscular tube that the stone passes through on its way from the kidney to the bladder. The stone irritates nearby nerves that share routes with the groin, lower belly, and even the genitalia when it reaches the9 lower ureter, which is closer to the bladder.Referred pain results from this, which means that you experience pain in places other than the actual location of the stone.

Urinating in pain - The stone aggravates the urinary system lining as it approaches or enters the bladder.This results in pressure and irritation, which makes it painful to urinate (a condition called dysuria).The stone may also induce a burning or stinging feeling if it partially blocks the urethra or scratches it when urinating.

Urine that is strangely colored, hazy, or smells - During a kidney stone incident, an odd or unpleasant urine odor could be caused by:
Urinary Tract Infection (UTI): Urine with a bacterial infection may smell strongly
and disagreeably.
Dietary Factors: The smell of urine can be changed by specific diet and drugs.Dehydration: Stronger odors may result from concentrated urine brought on by inadequate fluid consumption.[79]

Feeling queasy - Renal colic, which is one of the worst aches imaginable, is asevere, cramping ache that can be caused by kidney stones.

Your organs and brain are connected by the vagus nerve, which is activated by this pain and is part of the autonomic nervous system.This system's stimulation may result in lightheadedness, sweating, nausea, and vomiting.However, urinary tract infections (UTIs) are caused by bacteria that enter the urinary system and cause issues throughout the urinary tract, usually because of the Escherichia coli, or E. coli, bacteria that are found in your intestinal tract and in your feces. Women are more prone than men to experience them because of anatomical differences. Additional reasons:

Use of catheters - Particularly with prolonged use, catheter use dramatically raises the risk of UTIs. In UTIs, some urease-producing bacteria (such Proteus mirabilis) can increase urine pH, which encourages the development of struvite (infection-related) stones. A study showed that renal stones, hydronephrosis, and indwelling catheterization are substantially linked to UTIs caused by S. aureus.[80]

Having sex - Bacteria from sexual activity can enter the urethra and travel up to the bladder, where they can cause infection. Because of anatomical characteristics including a shorter urethra and its closeness to the anus and vagina, this is particularly true in women. [81]

Blockages in the urinary tract - Urinary tract obstructions, such those brought on by urethral strictures, urinary stones, or benign prostatic hyperplasia (BPH), can greatly raise the risk of UTIs. Infection is made easier by these impediments, which also result in increased

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bacterial colonization, reduced immunological clearance, and urine stasis.

Inhibition of the immune system - Complex immune system changes are linked to kidney stone illness (nephrolithiasis). Although kidney stones do not directly induce immune suppression, the immune system's instability and inflammatory reactions during stone development can cause immune cells to operate less well.[82]

Certain birth control methods - Hormonal birth control, such as tablets, patches, or injections, has not been shown to be a direct cause of kidney stones.But estrogen, a hormone found in many birth control tablets, may have an impact on calcium metabolism and raise the risk of calcium oxalate stones by increasing the excretion of calcium in the urine.[83]

Menopause - Increased urine calcium excretion, which affects calcium metabolism and is brought on by the postmenopausal drop in estrogen, is one of the primary risk factors for calcium-based kidney stones.[10, 84]

IV.REPEATED UTIS AND KIDNEY STONES ARE CLOSELY CONNECTED. HERE'S HOW.

Stagnation of urine

Kidney stones can prevent urine from flowing normally. Your urinary tract becomes a haven for bacteria when urine remains stagnant. The recurrence of UTIs and infections might result from this stagnant urine.

Development of bacteria

Furthermore, kidney stones can produce crevices and cracks that allow bacteria to hide and grow. The germs may spread to other areas of your urinary tract, such as your bladder and urethra, as they develop.

The immune reaction

Additionally, kidney stones may cause your body to mount an immunological defense. Inflammation can both worsen kidney stones and aid in their creation, according to researchers. You may be more prone to recurring UTIs if kidney stone-induced inflammation and irritation impair your body's natural defenses against infections.[11]Figure - 02 represents how the kidney stone caused due to repeated urinary tract infection

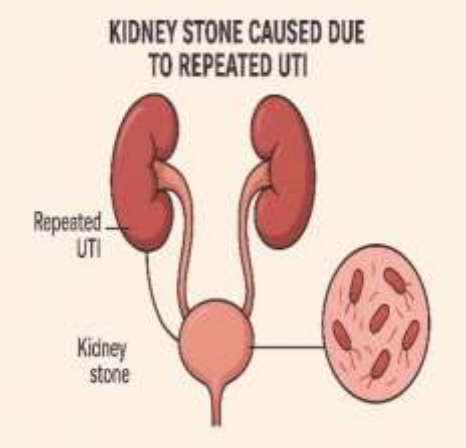

Fig 2 :Kidney stone caused due to repeated UTI

V. PATHOPHYSIOLOGY:

Kidney stones are generally categorized into two primary types: those that contain calcium (calcareous) and those that do not (non-calcareous) [12]. Approximately 75% of kidney stones are radio-opaque, meaning they are visible on X-rays due to their calcium content. These stones are primarily made up of calcium oxalate (CaOx) or calcium phosphate (CaP). Less common stone types include carbapatite (15.6%), uric acid stones (urate, 12.4%), struvite—a compound of magnesium ammonium phosphate (2.7%)—and brushite (1.7%) [13].The mechanics behind the production of renal stones are controversial and typically presented as a multi-step, intricate process . Urine supersaturation is the first step in this

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process,This is accompanied by renal retention, growth, aggregation, and crystal nucleation. Nevertheless, non-stone formers have also reported experiencing similar occurrences [14], supporting a multiple etiology theory [15]. According to recent research, nephrolithiasis should be considered a systemic disease because of the way several risk variables interact [16].Modifiable risk factors for nephrolithiasis include The body-mass index (BMI), calcium and hydration levels, and sugar-sweetened beverage consumption [17].

Calcium-containing stones are primarily composed of either CaOX (50%) or CaP (5%), or both (45%)(14).

It has been reported that diet and the development of CaOX stones are strictly correlated [12].Increased natriuresis and calcium excretion in the urine are caused by consuming more salt. In a similar vein, greater oxalate ingestion may result in increased oxaluria. Furthermore, consuming more animal protein and sulphated amino acids causes urine to become more acidic, which promotes the production of stones [12].Urinary oxalate excretion is higher in vegetarians than in people who eat a typical mixed diet [18]. Therefore, persons with mild hyperoxaluria might not benefit from a vegetarian diet if they do not get enough calcium. The likelihood of developing nephrolithiasis is linked to certain nutrition-dependent disorders, Epigenetic modulation has been proposed as a partial explanation for the differential impact of modifiable risk variables on stone formation [12].such as obesity, metabolic syndrome, diabetes, and insulin resistance, the relationship between which cannot be adequately and mechanistically described [12].

It is known that CaOX stones come in two main varieties: Both CaOXdihydrate (COD) and CaOX monohydrate (COM), or a mix of the two [14]. Compared to COD, COM is more commonly observed and is the most stable crystal form. COD has a higher solubility than COM in the human body's interior environment. As a result, the supersaturation of COM is always higher than that of COD [25].The emergence of such kidney stones is more likely to be explained by the nucleation and development of COD crystals in the early phases of stone formation [25]. After then, beginning in the middle of the COD stone, COD progressively changes into COM.Highsupersaturation levels for both the stable and metastable phases cause the preferred nucleation of crystals in the metastable phase because of its lower interface energy, which explains the prior nucleation of COD [25]. Consequently, the dissolution of COD crystals is required for the conversion from COD to COM, which is essentially a solution-mediated process [25]. Urine's COM and COD supersaturation levels, however, continuously stay high enough for calcium oxalate crystals to form.Furthermore, the surface of a kidney stone is continuously exposed to urine, which eliminates the possibility of COD and COM dissolution [25]. In the case of a kidney stone with COD, many COD crystals accumulate, resulting in multiple gaps between the crystals within the stone [25]. Quantitative mass spectrometry studies revealed a wide variety of proteins contained within the COM matrix [26]. Such proteins may stimulate COM aggregation based on polyanion–polycation aggregation based on electrostatic attraction [27]. This theory is supported by earlier research that demonstrated how protein aggregates can contribute to CaOx crystal aggregation and nucleation [28,29].

Urine's COM and COD supersaturation levels, however, continuously stay high enough for calcium oxalate crystals to form.Furthermore, the surface of a kidney stone is continuously exposed to urine, which eliminates the potential disintegration of COM and COD [25]. When a stone in the kidney with COD forms, a large number of COD crystals build up, creating several spaces between the crystals [25]. Numerous proteins included in the COM matrix were identified by analytical mass spectrometry studies [26]. According to polyanion–polycation formation based on electrostatic attraction, these proteins might promote COM aggregation [27]. Previous studies that showed how aggregates of proteins can aid in CaOx crystal accumulation and nucleation [28,29] lend credence to this notion.(28,29)

After the aggregation,the stone will be formed and due to the formation of stone there will be obstruction of the flow of urine. And urine starts to stagnant at that place. Due to this there will be development of bacteria. The risk of bacterial overgrowth increases with the amount of time urine stays stagnant. Sometimes recurring UTIs are the specific cause of struvite stones [30]. Figure -03 represents the pathophysiology of the kidney stone and urinary tract infection

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 381-393 www.ijprajournal.com ISSN: 2456-4494

Fig 3: Pathophysiology of kidney stone and UTI

Modern Pathophysiological Concepts for Urinary Tract Infections

Microbiota in Urine;

The term microbial ecosystem describes the complete array of bacterial DNA, hereditary material, and the biochemical substances they generate., whereas the term "microbiota" describes the microorganisms that reside inside an individual [67]. Due to the technical difficulty of determining the entire range of bacterial species, urine has been generally recognized as sterilized in healthy humans. However, many microbes can now be detected because of technological and molecular biology advancements [68,69].However, only 30% of patients with symptoms received positive results using regular urine culture refers to a study that evaluated typical urinary cultures using future DNA sequencing, [70 , 71]. The development of some diseases may be significantly impacted by the identification of a particular bacterium in the urine. Standard urine cultures were typically used in earlier research, which had significant drawbacks for detecting the entire range of bacterial species. The expanded quantitative urine culture (EQUC) technology has rapidly advanced [72]. Instead of the sole UPEC that is regularly found on a typical urine culture , UTI symptoms may be caused by anaerobic bacteria or a multimicrobial infection, according to urine culture findings that are negative [73–74].More than 90% of the non-UPEC used by EQUC was overlooked by the conventional urine culture method, according to Price et al. [75].

It is commonly believed that periurethral contamination by gut-dwelling microorganisms is the cause of UTIs. One could think of periurethral infections by a gut pathogen as the initial stage, which is followed by bladder colonization. But there isn't much evidence to back up the theory. In fact, a recent study found that the E. coli strains in the urine and feces of women with UPEC differed [76]. There is very little information available regarding the traits of pathogenic genes that contribute to the tendency of intestinal E. coli strains to cause UTIs [77]. On the other hand, another study has shown how crucial pili and flagella are to the UPEC invasion process [78].

VI. DIAGNOSTIC APPROACH:

Blood tests: Blood test need to be done to find out if there is too much uric acid or calcium in the blood. The results of a blood examination can assist medical professionals in keeping an eye on kidney health and could lead them to search for further health problems [55].

Urine testing: If your kidneys discharge too many minerals that can cause stones or not enough compounds that prevent them, a 24-hour collection of urine test can tell you. The physician could advise taking a minimum of two urine samples over the course of two days for this test [56].

Imaging tests: It could indicate that kidney stones are present in the stream of urine. Basic abdomen X-rays that might overlook little kidney

An Analysis of Kidney Stone and Herbal Remedies High-speed or dual-energy digital imaging (CT),

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 381-393 www.ijprajournal.com ISSN: 2456-4494

which can identify even tiny stones, takes the position of 201 stones [57]. Ultrasonography, a non-invasive test that requires inserting dye into an arm vein and taking CT images (CT urogram) or X-rays (intravenous pyelogram)There is also the potential of imaging while the dye passes through the bladder and kidneys [58,59].

VII.TREATMENT AND PREVENTION OF KIDNEY STONES:

The pH of urine and 24-hour urine examination provides details regarding factors that can contribute to stone formation and can guide prevention whenever stone formation cannot be removed. Patients should be informed about the hazards of using medications that raise the risk of kidney stones, such as diuretics, antibiotics, and protease inhibitors.(21)

Alternative and Complementary Medicine:

Non-mainstream practices are referred to as "alternative" when they are employed in place of conventional medicine or as "complementary" when they are used in conjunction with it.

Many kidney stone patients use complementary and alternative medicine (CAM) to relieve their symptoms or lower their risk of recurrence. The inability to stick to dietary modifications, the adverse effects of pharmaceuticals, the affordability, and the confidence in the safety of CAM treatments are some of the factors contributing to the use of CAM in the renal stone population [4]. According to Koo et al., there is either insufficient or inconsistent scientific proof to support the claims made by around two-thirds of supplements that are claimed to treat or avoid kidney stone formation (22)

VIII.HERBAL PRODUCTS:

GREEN TEA: The herb green tea (Camellia sinensis) has long been utilized as a herbal remedy because of its abundant polyphenols, which make it a potent antioxidant [44].Green tea has drawn a lot of attention for use as a dietary supplement in patients with nephrolithiasis and urinary stones because of its anti-lithogenic, anti-atherosclerotic, and antioxidant properties, despite the fact that it is an oxalate-rich natural agent and cannot be advised for renal calculi caused by calcium oxalate[45,46,47]. The presence of polyphenols and other phytochemicals in green tea is probably what gives it its protective properties. Green tea catechins that offer protection against oxalate-induced toxicity include epicatechin gallate (ECG), epicatechin gallate (EGCG), epicatechin gallate (GGC), and epicatechin (EC). Supplementing rats with green tea reduced excretion and prevented the formation of crystals in their kidneys.(22)

Rosemary (Rosmarinus officinalis)

Portugal and other temperate Mediterranean nations are the native home of rosemary. Numerous pharmacological effects were discovered in theextracts from this plant, such as those with antibacterial, antioxidant, anti-inflammatory, analgesic, and antidiabetic properties.(61,62)

Rosemary extracts are highly helpful at combating bacterial infections, such as urinary tract infections, because of their strong anti-oxidative action and immune-boosting qualities.(63)

The majority of common bacterial pathogens that cause UTIs, including E. coli, K. pneumoniae, P. mirabilis, P. vulgaris, P. aeruginosa, and S. aureus, were susceptible to the antibacterial activity of rosemary extracts.(64)

Cinnamon (Cinnamomum verum)

Cinnamon belongs to the Lauraceae family and has antibacterial and antioxidant qualities. Proanthocyanidins, eugenol, trans-cinnamyl acetate, and trans-cinnamaldehyde are among the bioactive phytochemicals that have been utilized to treat urinary tract infections.[66].

Amalaradjou et al. demonstrated that by downregulating key virulence genes in the bacteria, trans-cinnamaldehyde, an essential oil, might prevent the proliferation of E. coli bacterial accumulation on catheter surfaces.

Essential oils have antibacterial properties through a number of mechanisms: (I) because they are hydrophobic, they might target the lipid-containing bacterial cell membrane and mitochondria and change the permeability, which ultimately causes ions and other cell contents to leak; (II) they may inhibit the production of energy and the uptake of glucose; and (III) they may inhibit the activities of crucial enzymes like amino(65)

IX.SYNTHETIC DRUGS :

Citric acid and thiazide are frequent calcium SFs.

To date, citrate of potassium salts have been the subject of three prospective trials, two of which have shown therapeutic effect .(48,49)In contrast to the two earlier investigations, the control subjects in the third study experienced

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fewer stone formations. and it does not use a double-blind approach. Every participant had hypocitraturia and was a CaOx SF. Three randomised, controlled, double-blind trials have been conducted to examine thiazide diuretic medications.(50) Equivalent findings were obtained when chlorthalidone was administered at either 25 mg or 50 mg daily (51, 52). . The therapeutic effects of indapamide and hydrochlorothiazide were comparable to those of chlorthalidone. (24,)

Calcium Intake and The supplementation in the Diet

Dietary calcium intake is essential for maintaining homeostasis in the body. The amount of calcium consumed affects a number of systems, including intestinal function, the functioning of muscles, kidney function, bone health and growth, intestinal functioning, glycolysis and gluconeogenesis, and parathyroid gland function [53]. As previously stated, renal calcium resorption is impaired in idiopathic hypercalciuria, which may result in an abnormal calcium balance and a higher risk of nephrolithiasis [54]

A synthetic medication used to treat diseases of the stones [59,60]

1. Diuretics: Amiloride (Midamor)
2. Allopurinol: A substitute for hypoxanthine (Lupurin, Zyloprim)
3. Bile acid sequestrants Cholestyramine (Questran).
4. Derivatives of bile acid and cholic acid
5. Digoxin, a cardiac glycoside (Lanoxin)
6. Bisphosphonate etidronate disodium
7. The statin fluvastatin (Lescol)
8. Gemfibrozil: Derivatives of fibric acid
9. Peptidomimetichydroxyethylene, or indinavir
10. Derivatives of Zonisamide and Sulphonamide.

The image(Figure -04) below illustrate the mechanism of action and the medications used to treat kidney stones brought on by urinary tract infections.

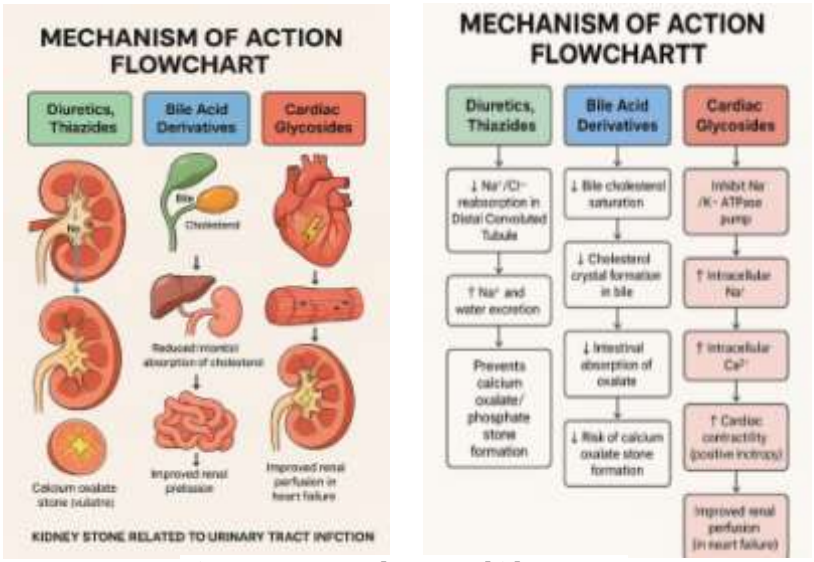

Fig 4: Drugs used to treat kidney stone

X. CONCLUSION:

A thorough and interdisciplinary approach is necessary to address the clinical issue posed by the complex link between renal stones and UTIs. In addition to increasing the likelihood of developing some kidney stones, particularly struvite, recurrent UTIs also make managing them more difficult and can result in a recurrent pattern of infection and stone recurrent. Effective prevention and therapy depend on an understanding of the underlying pathophysiology mechanisms, such as urease-producing bacterial activity and biofilm development.

To guide the right therapy, an accurate diagnosis using imaging, urine tests, and the composition of stones assessment is essential. Depending on the type of stone and the cause of the infection, pharmacological treatments such as urinary alkalinization, targeted antibiotic therapy, and inhibition of crystallization should be customized. For individuals with obstructing or

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Volume 10, Issue 4 July-Aug 2025, pp: 381-393 www.ijprajournal.com ISSN: 2456-4494

recurrent stones, surgical therapy is still essential, especially in cases where infection is involved.

Future treatment plans should integrate metabolic assessment, antibiotic stewardship, and individualized therapy regimens to interrupt the infection-stone cycle. For patients with both UTIs and nephrolithiasis, early treatment, education of patients, and long-term follow-up are essential to lowering recurrent infections, minimizing complications, and enhancing overall results.

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