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THE EPIDEMIOLOGY OF CALCIUM OXALATE UROLITHIASIS AND THE ROLE OF RENAL EPITHELIAL CELLS

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ABSTRACT

Calcium oxalate (CaOx) stones appear as the prevalent type of kidney stones which collectively form a substantial portion of the worldwide urolithiasis issue. The complete mechanisms which control the development of CaOx kidney stones have not been completely revealed by extensive research. The research analyzes CaOx stone pathophysiological mechanisms through kidney epithelial cells (KECs) involvement in crystal adhesion while investigating inflammation and

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apoptosis and analyzing oxidative stress. The study examines crucial risk elements beginning with inherited tendencies and continuing with food-related factors together with metabolic dysfunctions while investigating possible treatment options. The mechanisms of CaOX stone formation received evaluation through an extensive analysis of experimental studies and recent publications. The research report describes the Stone development process through observations of crystal nucleation mechanisms and monitoring of urinary pH adjustments and solution supersaturation quantities. The research specifically examines how KECs affect cellular responses to crystalline adherence together with their reaction to oxidative stress and apoptotic mechanisms. Researchers evaluate the successful preventive and therapeutic management techniques of KECs which encompass dietary adjustments alongside pharmacological therapy and forward-looking treatment approaches. CaOx stone development depends on urinary supersaturation along with crystal aggregation and how cells in the renal epithelium interact with each other. KECs actively control the development of inflammatory reactions and oxidative pressure together with apoptosis pathways to influence stone formation. The metabolism of oxalate along with calcium control and oxalate regulation experience influence from inherited risk factors eating patterns and gut microbial activity. The prevention of stone recurrence becomes possible through three key methods including fluid consumption boost and restrictive **oxalate diets** along with probiotic treatments.

KEYWORDS: Calcium oxalate stones, Urolithiasis, kidney stones, renal epithelial cells

INTRODUCTION

One of the first illnesses recognized by medicine is kidney stone disease, also referred to as urolithiasis or nephrolithiasis. An estimated 1–15% of people may have kidney stones at some point in their lives, and the incidence and prevalence of kidney stones are said to be rising globally. According to a recent study, kidney stones are present in approximately 1 in 17 individuals, with a frequency of 5.8% among them (6.5% in men and1 5.1% in women) [1]. Failure to address kidney stones properly leads to the blockage of the ureter pipe resulting in blood appearance in urine and frequently causing persistent urinary tract infections and also vomiting and painful urination while placing the kidneys at risk for permanent damage. The prevalence of urolithiasis has been rising worldwide during several decades. Urolithiasis

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develops into a recurring illness that affects patients at least half of the time within five to ten years and up to three-quarters of all patients within twenty years. Research indicates that various environmental elements linked to dietary changes and lifestyle behaviors as well as global warming will drive an increase in kidney stones [2]. Researchers have not yet determined what factors contribute to the rising occurrence of urolithiasis as well as its repeated outbreaks. The high occurrence rate of kidney stones among working-age people leads to substantial impacts on individual patients along with social consequences. It has also become a public health concern, especially for populations living in hot and arid climates. According to their mineralogical makeup, kidney stones may 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%). The two main types of kidney stones are calcareous (containing calcium) and non-calcareous. Calcium phosphate (CaP) and calcium oxide (CaOx), either separately or in combination, are the most prevalent forms of kidney stones in humans [3]. These stones are radio-opaque and calcareous. Randall's plaques (RPs), a CaP foundation, are where kidney stones originate. They start at the basement membranes of the loop of Henle's thin limbs on the surface of the renal papillaries. Men are more likely to have CaOx and urate stones, whereas females are more likely than men to have carbapatite and struvite stones [4]. There remains uncertainty about how gender differences influence the biological causes linked to urinary stone development. The development process of kidney stones includes urinary super-saturation alongside crystal nucleation and development and aggregation until formation regardless of stone composition. Kidney stones frequently develop in diabetic or obese individuals who have cardiovascular disease or hypertension as well as those suffering from metabolic syndrome [5]. Patients who experience nephrolithiasis also known as kidney stone formers (KSF) develop an increased risk of hypertension alongside chronic kidney disease (CKD) and end-stage renal disease (ESRD). A variety of promotive elements known to affect kidney stone formation collectively demonstrate strong effects of inhibition and promotion. Laboratory studies have shown that the protease inhibitor Inter-α-inhibitor (IαI) blocks CaOx crystals from forming in test tubes whereas of these study results indicate that kidney stone formation is promoted by hyperoxaluria hyperuricosuria and phosphaturia [6]. Medical

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practitioners consider calcium oxalate stones significant because they both tend to return after treatment and lead to chronic kidney disease (CKD). The pathophysiological processes that form calcium oxalate stones heavily depend on the first step of forming supersaturated conditions of calcium and oxalate in the urine [7]. Research shows stone recurrence affects half of all patients throughout a ten-year period because treatment and diagnostic methods have not yet effectively reduced this recurrence frequency. Furthermore, because repeated stones are linked to increasing renal damage, an increased risk of infection, and possible impairment of kidney function, the burden of nephrolithiasis goes beyond acute episodes [8]. Therefore, developing successful preventative and treatment techniques requires a knowledge of the molecular and cellular processes behind calcium oxalate stone development. Kidney epithelial cells play a crucial role in kidney stone formation by directly interacting with crystals in the urine, allowing them to adhere to the cell surface, get internalized, and potentially aggregate into larger stones,

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particularly when the epithelial cells are damaged or dysfunctional; this interaction between crystals and epithelial cells is considered a key mechanism in the development of kidney stones. Recent studies have highlighted the crucial involvement of renal tubular epithelial cells in the initiation and progression of calcium oxalate stone formation [9, 11]. These cells serve as key regulators of urinary composition and play an integral role in preventing crystal deposition. However, under pathological conditions, kidney epithelial cells undergo oxidative stress, inflammation, and apoptotic changes, creating a favorable environment for crystal adherence and stone growth. Oxalate crystals that contact renal tubule epithelial lining initiate both inflammatory reactions and cell destruction and cytokine secretion that contributes to stone development [10]. The absence of protective elements nephrocalcin along with Tamm-Horsfall protein enhances the formation and adhesion of calcium oxalate crystals. The identification of

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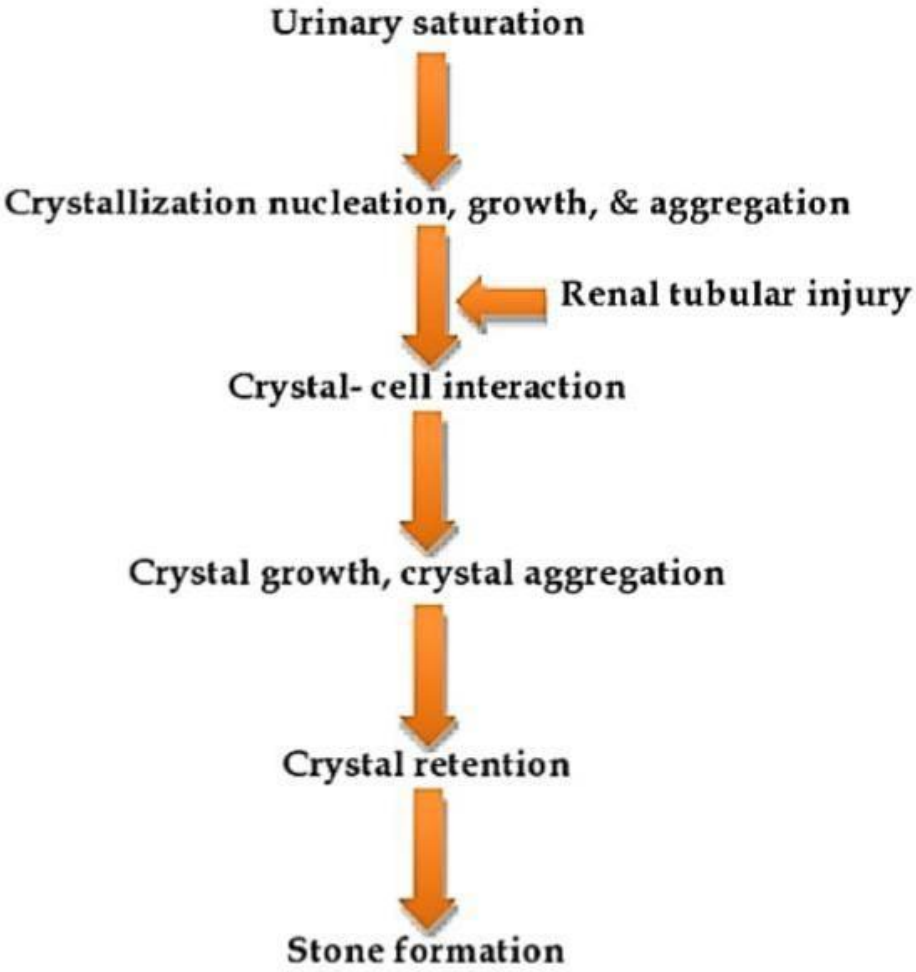
new therapeutic targets for kidney stone prevention requires a deep understanding of cellular processes.



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Researchers have extensively studied nephrolithiasis although several aspects regarding calcium oxalate stone formation require enhanced understanding. The current study research on how dietary components and metabolic problems and kidney epithelial cell damage affect each other. The study examines CaOx stone processes by analyzing epithelial cell function during crystal adhesion followed by the mechanisms of inflammation and oxidative stress. The study analyzes medication and prevention methods which influence the functions of kidney epithelial cells. New prevention approaches for calcium oxalate nephrolithiasis will be developed through this investigation of insufficient knowledge about prevention.

2. Pathophysiology of Calcium Oxalate Stones Formation

The most prevalent type of kidney stones consists of Calcium oxalate (CaOx) which represents between 70 to 80 percent of cases. Knowledge about how kidney stones develop and their typical signs and elements which cause stone formation remains essential to stop and manage this medical condition. This section will provide an overview of the mechanisms behind the formation of CaOx stones, the factors that increase the risk of their development, and the clinical approach to diagnosing them.

2.1 Mechanism of stone formation

The risk of stone formation increases when a crystal nucleates to grow into a larger particle within an individual whose urinary characteristics already display high stone development potential. Stones appear throughout multiple areas of the urinary tract including kidneys to ureters and bladder and urethra and other places. Research shows that stones develop due to genetics as well as nutrition patterns and lifestyle choices and medical diseases that involve metabolic abnormalities or urinary tract infections [12, 5].

The urinary tract stone starts to develop more crystals and simultaneously moves through the body producing various symptoms and discomfort. The dimensions together with chemical features of stones determine how easily they move through the urinary system. Small stones can

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typically transfer through the urinary system independently but medical intervention becomes necessary for treating larger stones [14, 2].

2.2 Urinary Supersaturation

Kidney stones start when the urine contains excess chemicals including calcium and oxalate and phosphate beyond their solubility threshold. This phenomenon is known as urinary supersaturation. A state of urine supersaturation develops because the chemical concentration surpasses the dissolving limit leading to crystal development. Small crystal particles form because the excess solution substances cannot stay dissolved during this condition while they naturally cluster together [13]. Minimal crystal particles eventually form kidney stones through their accumulation process to create large crystal formations.

Supersaturating conditions in urine affect kidney stone development through crystal formation processes and affect multiple other factors related to both crystal size and urine acidity together with crystal growth facilitators. The development of kidney stones requires knowledge about factors that cause urine supersaturation and crystal formation processes.

2.3 Crystal nucleation

The nucleation process stands as the critical component for crystal formation when starting from a supersaturated solution. A stable nucleus develops through the aggregation of solute molecules or ions which provides the base for crystal formation. The creation of an identifiable lattice pattern results in a crystal structure. Crystal development happens both on surfaces like cells and extracellular matrix and within small areas within solution gaps which exist in selected nephron segments [30]. Nucleation occurs through heterogeneous mechanisms on solid surfaces or foreign particles yet also through homogeneous mechanisms within the solution framework [15, 16].

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2.4 Growth of crystals

Once nuclei form crystals allow new molecules to enter their crystal lattice structure which results in expansion. The rates of crystal formation depend on urine salts concentration and pH values together with substances that promote or inhibit crystalation [32]. The crystal aggregation process along with growth is suppressed by growth inhibitors which comprise citrate and magnesium that connect to crystal surfaces thus arresting crystal development [3]. The surface charge elevation and inter-crystal adherence of crystal growth promoters such as calcium and oxalate leads to aggregation and growth of crystals [12].

2.5 Aggregation of crystals

The continuous aggregation of crystals leads to larger particles which eventually results in stone formation. Among the variables influencing crystal aggregation are stone-causing salts along with their concentrations and urine pH levels and both organic and inorganic substances which may act as aggregate barriers or crystal growth inhibitors [2, 7]. The development of stones depends on urine flow rates because greater flow speeds crystals away from forming aggregates whereas low flow allows crystals to grow larger through aggregation [5].

2.6 Interaction between crystal and cell

The pathophysiology of kidney stones heavily depends on crystal adhesion to renal epithelial cells. Kidney crystals create damage and inflammation in cells whenever they stick to their outer surfaces. The technique attracts immune cells and releases inflammatory mediators which along with the crystal development contributes to their aggregation. Three factors allow crystals to bind to renal cells—the surface receptors and extracellular matrix proteins along with electrostatic interactions. Crystals that have bound to cells generate multiple forms of cellular damage through pathways such as mitochondrial dysfunction and oxidative stress along with membrane damage [9]. Crystal-induced damage together with inflammation receive greater intensity because of these modifications which in turn release danger signals and activate inflammatory

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pathways. Crystals along with renal cells and immune cells result in urinary casts that can block urine flow while leading to stone formation. The development of kidney stone disease receives acceleration through the inflammatory cytokine and chemokine production activities of both immune cells and renal epithelial cells alongside T cells and macrophages. The inflammation-damage cycle enables stone accumulation that pushes kidney stone disease toward its emergence then progression.

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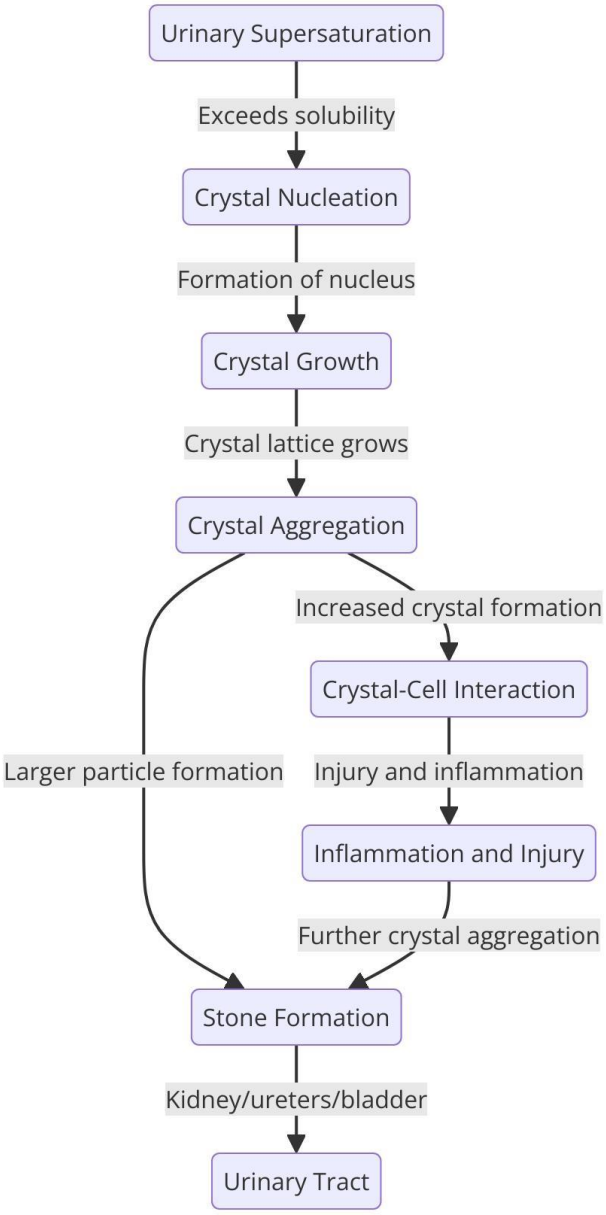

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3. Causes of Calcium Oxalate Stones

Calcium oxalate stones are the most frequent type of kidney stones, and their production is impacted by various variables, including dietary habits, metabolic diseases, genetic predisposition, and urine irregularities [17]. The primary reasons of calcium oxalate stone development include:

3.1. Dietary and Lifestyle Factors

One of the major factors in the rate of calcium oxalate stone development is a function of diet. Eating large amounts of oxalate from spinach, chocolate, beets, almonds, or rhubarb can increase urine oxalate and promote stone formation. This population is at increased risk with large excess of dietary oxalate intake from foods without adequate calcium intake facilitating greater intestinal absorption of oxalate [18]. Ironically, stones actually tend to form due to a low calcium diet. Calcium is a known dietary binder of oxalate and exhibits this effect by binding oxalate in the intestinal tract resulting in a decrease in its absorption and urinary excretion. Insufficient dietary calcium leads to excess free oxalate in the urine, which promotes both crystal nucleation and aggregation [19].

In addition, the consumption of high protein and sodium is much more conducive to stone formation. Animal proteins elevate the acid load of the body, which leads to calcium being released from bone and higher excretion of calcium in the urine. As a result, it creates an environment that is favorable for stone formation. Correspondingly, a salt-rich diet reduces intestinal calcium reabsorption that leads to renal calcium hyper-absorption which increases the risk of stones-forming as hypercalciuria is one of the most important risk factors for stones formation [20]. Similar is the lifestyle factor called dehydration that leads to concentrated urine resulting in crystal formation due to supersaturation of calcium and oxalate. Individuals in hotter locations are susceptible or individuals who do not consume adequate amounts of water. Forty-

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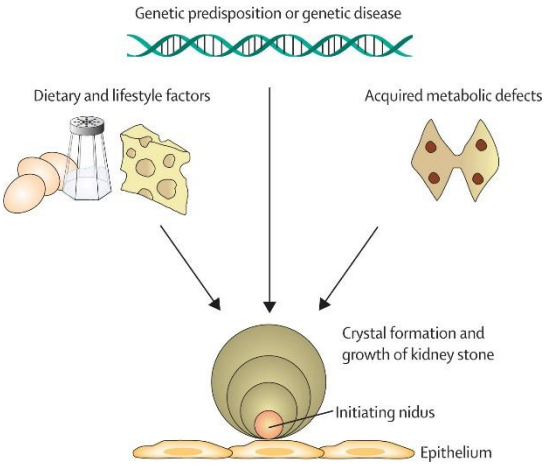
three percent (43%) of the survey respondents report that staying hydrated is one of the best ways to prevent stone recurrence [21].



3.2 Genetic and Metabolic Influences

The development of calcium oxalate nephrolithiasis heavily relies on both genetic background and metabolic abnormalities in patients. The condition of heightened oxalate excretion leads to stone formation risks and crystal development as primary inherited or secondary dietary and gut-related hyperoxaluria exists [22]. Excessive food intake or intestinal malabsorption produces secondary hyperoxaluria but primary hyperoxaluria exists as a rare genetic disorder that causes the liver to create excessive oxalate because of enzyme problems. The characteristic symptom of hereditary metabolic disorder hypercalciuria includes an elevated amount of urine calcium regardless of dietary calcium consumption. The likelihood of stone formation through calcium oxalate precipitation rises due to this condition [23].

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When accompanied by hypocitraturia metabolic disorder with its connection to low urine citrate levels stone formation becomes worse. A lack of citrate in the body promotes stone development because its natural process stops calcium crystals from forming clusters. The risk of developing uric acid stones along with mixed calcium oxalate stones increases in individuals who have gout and hyperuricemia because elevated uric acid levels exist [24].

3.3 Urinary and Systemic Disorders

The medical condition and urinary problems significantly impact the formation of stones throughout the body. The pH value of urine controls what type of stones form while alkaline levels increase calcium phosphate stones and acid levels trigger calcium oxalate crystal growth. The urinary composition changes due to renal illnesses together with continuous inflammation produce optimal conditions for stone formation [25].

The formation of stones gets significantly affected by various conditions present in gastrointestinal diseases. Intestinal absorption of calcium and oxalate undergo regular modifications among patients who have Crohn's disease, celiac disease and irritable bowel syndrome (IBS) and people who underwent gastric bypass surgery. Enteric hyperoxaluria functions as a disease that forces free fatty acids to bind with dietary calcium instead of oxalate to increase gut absorption of oxalate and thus raise urinary oxalate levels [26]. This medical condition substantially enhances the risk of calcium oxalate stone formation.

3.4 Role of Gut Microbiota in Oxalate Metabolism

Oxalate breakdown requires special bacterial strains while gut microbiome plays a vital role in managing oxalate metabolism levels. Oxalobacter formigenes stands as the most studied bacterial species regarding oxalate metabolism since it utilizes oxalate as its primary energy source thus lowering oxalate absorption and elimination through urine [27]. People become at higher risk of stone formation when they lack Oxalobacter formigenes in their bodies because of antibiotic use and gastrointestinal conditions or gut dysbiosis leading to elevated urine oxalate

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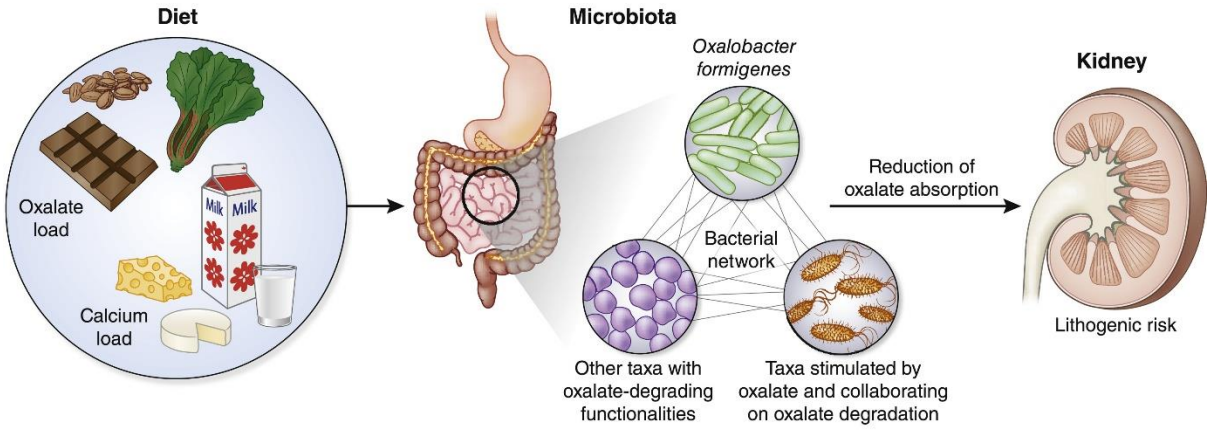
levels. The increasing popularity of microbiome-targeted therapies suggests bacteria-based probiotics have potential as a stone prevention method through breaking down oxalate [28, 5].



3.5 Key Causes and Their Effects

Cause	Mechanism	Effect on Stone Formation
High oxalate diet	Increases oxalate absorption	Promotes calcium oxalate crystallization
Low calcium intake	Increases oxalate availability	Enhances oxalate absorption in intestines
High salt intake	Reduces renal calcium reabsorption	Increases urinary calcium levels
Dehydration	Concentrates urine	Facilitates crystal supersaturation
Hyperoxaluria	Excess oxalate excretion	Enhances calcium oxalate crystal formation
Hypercalciuria	Increased urinary calcium	Promotes calcium oxalate supersaturation
Low urinary citrate	Reduces crystal inhibition	Increases calcium oxalate aggregation

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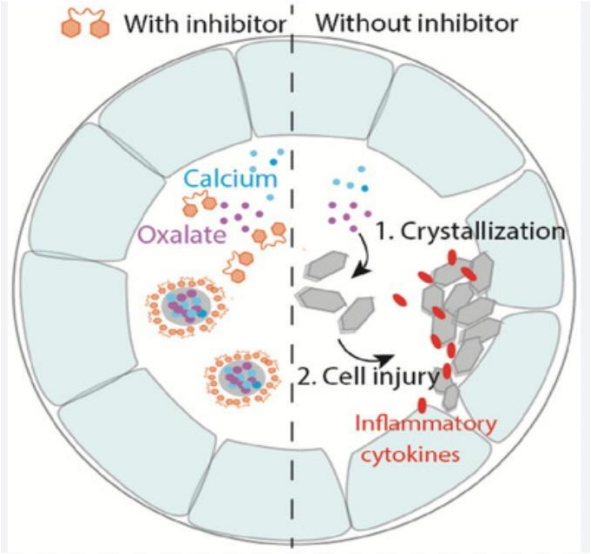
4. Role of Kidney Epithelial Cells in Calcium Oxalate Stone Formation

4.1 Crystal-Epithelial Cell Interactions

Multiple contacts between calcium oxalate (CaOx) crystals and kidney epithelial cells cause oxidative stress and inflammatory response that leads to cell damage [29]. Several stone-forming pathogenic processes begin after crystals attach to renal tubular epithelial cells (RTECs). Research confirms that epithelial cells damaged through contact with CaOx crystals trigger oxidative cell damage by producing reactive oxygen species (ROS). Apoptosis occurs together with mitochondrial dysfunction as a result of this process. The crystal-cell interaction leads to activation of nuclear factor-kappa B (NF-κB) alongside the NLRP3 inflammasome signaling pathways. The signaling pathways activate fibrosis along with inflammation that leads to stone development and stone retention [30]. When affected by oxidative stress the body boosts expression of adhesion molecules hyaluronan (HA) and osteopontin (OPN) to enhance CaOx crystal binding to renal epithelial tissue. The impaired ability of kidney cells to eliminate crystals becomes a factor that raises stone formation risk because of these chemical changes.



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4.2 Oxidative Stress and Apoptosis in Kidney Cells

Oxalate-triggered excessive ROS production leads to severe damage of kidney epithelial cells as a result of oxidative stress [31]. The kidney cells maintain their pro-oxidant-antioxidant equilibrium through the activities of Superoxide dismutase (SOD), catalase and glutathione peroxidase under normal conditions. The environment where stones develop causes an equilibrium shift which leads to damage of DNA and oxidative destruction of lipids along with dysfunctional mitochondria. Oxidative stress leads to apoptotic pathway initiation through mitochondrial instability which results in epithelial cell programmed death [32, 21]. Cellular injuries lead to damage of epithelial tissue which makes it easier for CaOx crystals to bind to the bare basement membrane. The stone formation process reaches higher severity with apoptotic cells while they serve as sites that promote crystal aggregate formation.

Oxidative Stress Marker	**Effect on Kidney Epithelial Cells**
Reactive Oxygen Species (ROS)	Increases apoptosis and inflammation
Mitochondrial Dysfunction	Reduces ATP production, leading to cell death
Lipid Peroxidation	Damages cell membranes, enhancing crystal adhesion
Glutathione Depletion	Weakens antioxidant defense, increasing susceptibility
Endoplasmic Reticulum (ER) Stress	Disrupts protein folding and cellular homeostasis

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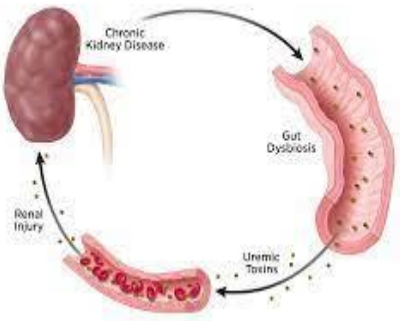
4.3 Cellular Injury and Inflammatory Response



Research indicates that kidney stone development relates directly to inflammatory responses particularly in how renal epithelial cells interact with CaOx crystals [33]. When kidney cells suffer crystal damage they produce inflammatory cytokines that primarily include IL-1β and TNF-α and IL-6. The activation of NLRP3 inflammasome in epithelial cells brings about elevated inflammation that invites both neutrophils and macrophages. The immune response preserves crystals through the production of ROS and inflammatory mediators that generally lead to aggravated tissue damage [34]. The body develops tubular fibrosis during chronic inflammation that leads to renal function deterioration and raises the probability of kidney stone relapse. The endoplasmic reticulum (ER) experiences increased stress when epithelial cells encounter high oxalate concentrations which disturbs cell homeostasis and causes oxidative damage.

Inflammatory Pathway	**Role in Stone Formation**
NLRP3 Inflammasome Activation	Triggers inflammatory cascades that promote crystal adhesion
NF-κB Pathway	Enhances expression of inflammatory cytokines
Cytokine Release (IL-1β, TNF-α)	Increases epithelial damage and oxidative stress

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Macrophage Recruitment	Exacerbates kidney injury via excessive immune response
Fibrosis Induction	Leads to tissue remodeling and long-term kidney dysfunction

4.4 Adhesion, Retention, and Stone Growth

The development of stones requires calcium oxalate crystals to bind with kidney epithelial cells. Crystal attachment occurs on the underlying extracellular matrix which serves as an adhesive surface because epithelial damage reveals this matrix. Sanction among stone-forming patients increases three different adhesion molecules known as Osteopontin, hyaluronan, and matrix metalloproteinases which boost crystal attachment effectiveness [35]. The renal tubules begin trapping large particles that form when crystals join together after binding. Nephrolithiasis develops progressively when crystals embedded in kidney tissue cause continuous inflammation together with oxidative stress. Stone formers show significant changes in their kidney microenvironment through increased tissue fibrosis combined with extended oxidative stress markers [5, 17].

4.5 Oxidative Stress, Epithelial Dysfunction, and Stone Pathogenesis

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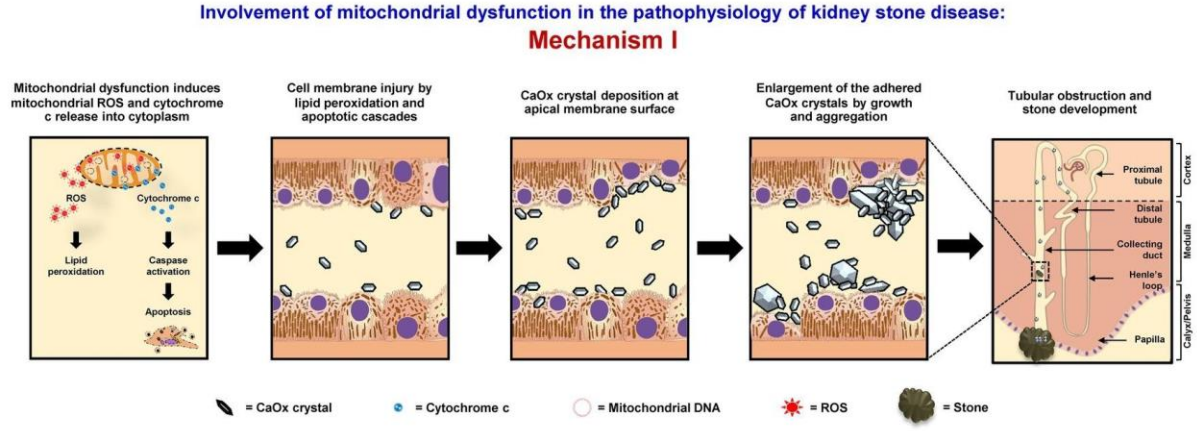
The main cause of epithelial cell damage in kidney stone disease results from mitochondrial



dysfunction. Oxalate or CaOx crystals trigger kidney epithelial cells to lower their mitochondrial membrane potential and reduce ATP synthesis and enhance apoptotic rates [32]. The development of kidney stones leads to enlarged and fragmented mitochondria that increases damage to affected cells researchers have observed. The modification of ion transport paths resulting from oxidative stress disrupts the renal cells' processing of calcium and oxalate. An excessive amount of intracellular calcium resulting from calcium channel irregularities leads to increased ROS formation and inflammatory pathways activation [26]. Renal epithelial cells within stone-forming areas experience increased exposure to harm because of simultaneous oxidative stress together with inflammatory damage and mitochondrial failure.

4.6 Molecular Pathways Involved in Epithelial Cell Damage

A number of molecular pathways are essential for the development of calcium oxalate stones and damage to kidney epithelial cells:

1. **NLRP3 Inflammasome Activation:** Triggers inflammatory cascades that promote stone retention and tissue damage.
2. **NF-κB Pathway:** Enhances the expression of pro-inflammatory cytokines, exacerbating epithelial injury [36].
3. **Oxidative Stress Pathways:** Overproduction of ROS leads to mitochondrial dysfunction and apoptosis.

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4. **Endoplasmic Reticulum Stress Response:** Disrupts protein folding and cellular homeostasis, worsening oxidative damage.

5. **Prevention and Management Strategies**

The prevention and treatment of calcium oxalate kidney stones are mainly through increasing the amount of fluid, changing the diet, and applying the medicine. Consumption of citrate-rich fruits can reduce stone formation, as can low-oxalate, normal-calcium diets [37]. Hydration is an important element that dilute urine solutes, and can reduce supersaturation and crystallization. Potassium citrate, a urinary alkalinizer, and thiazide diuretics are common pharmacological approaches for preventing stones by alkalizing the urine or reducing urinary calcium, respectively. Some probiotics such as the strain Oxalobacter formigenes with the proven ability to metabolize oxalate showed increased potential for its application, while novel treatment modalities are focusing on pathways of oxidative stress, inflammation and modification of gut microbiota [38]. Further personalization of treatment or prevention is being explored through techniques such as genetic screening for a stone-forming tendency to improve treatment outcomes.

Conclusion

Urolithiasis from calcium oxalate remains one of the most common multifactorial conditions while its distribution patterns react to genetic components and environmental along with nutritional elements. The formation and evolution of these stones heavily relies on renal epithelial cells because they control oxalate and calcium transport while starting inflammatory reactions and helping crystallization to occur. The interpretation of cellular-urinary solute interplay represents a fundamental requirement for generating preventive and therapeutic patient care strategies. Research on renal epithelial cell functions at a molecular level shows potential for revealing better methods to treat patients with calcium oxalate urolithiasis.

References

1. Peerapen, P., Boonmark, W., Putpeerawit, P., & Thongboonkerd, V. (2022). Calcium oxalate crystals trigger epithelial-mesenchymal transition and carcinogenic features in

renal cells: a crossroad between kidney stone disease and renal cancer. Experimental Hematology & Oncology, 11(1), 62.

2. Taguchi, K., Okada, A., Unno, R., Hamamoto, S., & Yasui, T. (2021). Macrophage function in calcium oxalate kidney stone formation: a systematic review of literature. Frontiers in Immunology, 12, 673690.
3. Sun, Y., Kang, J., Guan, X., Xu, H., Wang, X., & Deng, Y. (2021). Regulation of endoplasmic reticulum stress on the damage and apoptosis of renal tubular epithelial cells induced by calcium oxalate crystals. Urolithiasis, 49, 291-299.
4. Petrović, A., Kizivat, T., Bilić Ćurčić, I., Smolić, R., & Smolić, M. (2021). In vitro cell culture models of hyperoxaluric states: Calcium oxalate and renal epithelial cell interactions. Crystals, 11(7), 735.
5. Petrović, A., Kizivat, T., Bilić Ćurčić, I., Smolić, R., & Smolić, M. (2021). In vitro cell culture models of hyperoxaluric states: Calcium oxalate and renal epithelial cell interactions. Crystals, 11(7), 735.
6. Wang, Z., Zhang, Y., Zhang, J., Deng, Q., & Liang, H. (2021). Recent advances on the mechanisms of kidney stone formation. International journal of molecular medicine, 48(2), 1-10.
7. Taguchi, K., Okada, A., Unno, R., Hamamoto, S., & Yasui, T. (2021). Macrophage function in calcium oxalate kidney stone formation: a systematic review of literature. Frontiers in Immunology, 12, 673690.
8. He, Z., Liao, W., Song, Q., Li, B., Liu, J., Xiong, Y., ... & Yang, S. (2021). Role of ferroptosis induced by a high concentration of calcium oxalate in the formation and development of urolithiasis. International Journal of Molecular Medicine, 47(1), 289-301.
9. Allam, E. A. (2024). Urolithiasis unveiled: pathophysiology, stone dynamics, types, and inhibitory mechanisms: a review. African Journal of Urology, 30(1), 34.
10. Wigner, P., Bijak, M., & Saluk-Bijak, J. (2022). Probiotics in the prevention of the calcium oxalate urolithiasis. Cells, 11(2), 284.

11. Susilo, J., Purwanto, B., Doewes, M., & Indarto, D. (2021). Calcium Oxalate Crystals: Epidemiology, Causes, Modeling Of Crystal Formation and Treatment Management. Journal of Pharmaceutical Sciences and Research, 13(2), 118-123.
12. Negri, A. L., & Spivacow, F. R. (2023). Kidney stone matrix proteins: Role in stone formation. World Journal of Nephrology, 12(2), 21.
13. Zhao, Y., Yang, B., Yang, X., Zhou, H., Zhao, H., Yue, R., ... & Li, J. (2024). Exploring the Interplay between Calcium Oxalate Crystals and Renal Tubular Epithelial Cell Injury: Implications for the Formation and Prevention of Kidney Stones. Integrative Medicine in Nephrology and Andrology, 11(2), e23-00022.
14. Petrović, A., Kizivat, T., Bilić Ćurčić, I., Smolić, R., & Smolić, M. (2021). In vitro cell culture models of hyperoxaluric states: Calcium oxalate and renal epithelial cell interactions. Crystals, 11(7), 735.
15. Susilo, J., Purwanto, B., Doewes, M., & Indarto, D. (2021). Calcium Oxalate Crystals: Epidemiology, Causes, Modeling Of Crystal Formation and Treatment Management. Journal of Pharmaceutical Sciences and Research, 13(2), 118-123.
16. Zhao, Y., Yang, B., Yang, X., Zhou, H., Zhao, H., Yue, R., ... & Li, J. (2024). Exploring the Interplay between Calcium Oxalate Crystals and Renal Tubular Epithelial Cell Injury: Implications for the Formation and Prevention of Kidney Stones. Integrative Medicine in Nephrology and Andrology, 11(2), e23-00022.
17. Susilo, J., Purwanto, B., Doewes, M., & Indarto, D. (2021). Calcium Oxalate Crystals: Epidemiology, Causes, Modeling Of Crystal Formation and Treatment Management. *Journal of Pharmaceutical Sciences and Research*, *13*(2), 118-123.
18. Coello, I., Sanchis, P., Pieras, E. C., & Grases, F. (2023). Diet in different calcium oxalate kidney stones. *Nutrients*, *15*(11), 2607.
19. Alhamdi, M. H., & Alimah, G. J. (2024). Low Oxalate Diet for Prevention of Kidney Stone Disease: A Literature Review. *SCRIPTA SCORE Scientific Medical Journal*, *6*(1), 28-37.

20. Ghoneim, S. H., Alghaythee, H., Alasmari, B., & Safdar, O. Y. (2024). Impact of diet on renal stone formation. *Journal of Family Medicine and Primary Care*, *13*(11), 4800-4809.
21. Wang, X., & Wang, Q. (2024). Current Dietary and Medical Prevention of Renal Calcium Oxalate Stones. *International Journal of General Medicine*, 1635-1649.
22. Singh, P., Harris, P. C., Sas, D. J., & Lieske, J. C. (2022). The genetics of kidney stone disease and nephrocalcinosis. *Nature Reviews Nephrology*, *18*(4), 224-240.
23. Demoulin, N., Aydin, S., Gillion, V., Morelle, J., & Jadoul, M. (2022). Pathophysiology and management of hyperoxaluria and oxalate nephropathy: a review. *American Journal of Kidney Diseases*, *79*(5), 717-727.
24. Rahimnia, R., Mohammadi, A., Pakdel, A., Gholamnejad, M., Zemanati, E., & Khoshchehreh, M. (2025). Molecular biology, genetic, and epigenetic urolithiasis. In *Genetics and Epigenetics of Genitourinary Diseases* (pp. 139-149). Academic Press.
25. Tamborino, F., Cicchetti, R., Mascitti, M., Litterio, G., Orsini, A., Ferretti, S., ... & Schips, L. (2024). Pathophysiology and main molecular mechanisms of urinary stone formation and recurrence. *International Journal of Molecular Sciences*, *25*(5), 3075.
26. Siener, R., Ernsten, C., Welchowski, T., & Hesse, A. (2024). Metabolic Profile of Calcium Oxalate Stone Patients with Enteric Hyperoxaluria and Impact of Dietary Intervention. *Nutrients*, *16*(16), 2688.
27. Al-Kabe, S. H., & Niamah, A. K. (2024). Current Trends and Technological Advancements in the Use of Oxalate-Degrading Bacteria as Starters in Fermented Foods—A Review. *Life*, *14*(10), 1338.
28. Nazzal, L., Francois, F., Henderson, N., Liu, M., Li, H., Koh, H., ... & Blaser, M. J. (2021). Effect of antibiotic treatment on Oxalobacter formigenes colonization of the gut microbiome and urinary oxalate excretion. *Scientific reports*, *11*(1), 16428.
29. Deng, Z., Tan, J., Zhang, R., Zeng, J., Yin, G., & Jiang, X. (2022). Mechanism and influencing factors of crystal-cell interaction in the formation of calcium oxalate stones. *Zhong nan da xue xue bao. Yi xue ban= Journal of Central South University. Medical Sciences*, *47*(5), 555-561.

30. Gao, M., Meng, T., Chen, F., Peng, M., Li, Q., Li, L., ... & Yang, X. (2024). Inhibitory effect of Incarvillea diffusa Royle extract in the formation of calcium oxalate nephrolithiasis by regulating ROS-induced Nrf2/HO-1 pathway in rats. *Journal of Ethnopharmacology*, *325*, 117619.
31. Ye, T., Yang, X., Liu, H., Lv, P., Lu, H., Jiang, K., ... & Tang, K. (2021). Theaflavin protects against oxalate calcium-induced kidney oxidative stress injury via upregulation of SIRT1. *International Journal of Biological Sciences*, *17*(4), 1050.
32. Su, B., Ren, Y., Yao, W., Su, Y., & He, Q. (2024). Mitochondrial dysfunction and NLRP3 inflammasome: key players in kidney stone formation. *BJU international*, *134*(5), 696-713.
33. Sun, Y., Sun, H., Zhang, Z., Tan, F., Qu, Y., Lei, X., ... & Liu, H. (2024). New insight into oxidative stress and inflammatory responses to kidney stones: Potential therapeutic strategies with natural active ingredients. *Biomedicine & Pharmacotherapy*, *179*, 117333.
34. Torres, S., Segalés, P., García-Ruiz, C., & Fernández-Checa, J. C. (2022). Mitochondria and the NLRP3 inflammasome in alcoholic and nonalcoholic steatohepatitis. *Cells*, *11*(9), 1475.
35. Chanthick, C., & Thongboonkerd, V. (2022). Hyaluronic acid promotes calcium oxalate crystal growth, crystal-cell adhesion, and crystal invasion through extracellular matrix. *Toxicology in Vitro*, *80*, 105320.
36. Carcaterra, M., & Caruso, C. (2021). Alveolar epithelial cell type II as main target of SARS-CoV-2 virus and COVID-19 development via NF-Kb pathway deregulation: A physio-pathological theory. *Medical hypotheses*, *146*, 110412.
37. Finger, M., Finger, E., Bellucci, A., & Malieckal, D. A. (2023). Medical management for the prevention of kidney stones. *Postgraduate medical journal*, *99*(1169), 112-118.
38. Papatsoris, A., Alba, A. B., Galán Llopis, J. A., Musafer, M. A., Alameedee, M., Ather, H., ... & Tuerk, C. (2024). Management of urinary stones: state of the art and future perspectives by experts in stone disease. *Archivio italiano di urologia, andrologia: organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica*, *96*(2), 12703.