

REVIEW ARTICLE

Molecular Disruptions in Calcium and Oxalate Homeostasis: The Integrative Biology of Nephrolithiasis

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ABSTRACT

Nephrolithiasis is a progressively prevalent urological condition, impacting 12-13% of the global population. Calcium oxalate (CaOx) stones account for 75% or more of all stone types. It is a multifactorial illness that predominantly occurs when metabolic disturbances modify the composition of urine solutes. The metabolic abnormalities encompass hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria. Hypercalciuria caused by mutations in VDR, CaSR, and claudin. These factors collectively improve intestinal calcium absorption, bone resorption, and renal reabsorption. Hyperoxaluria is characterized by deficits in the enzymes AGXT, GRHPR, and HOGA, along with mutations in the genes SLC26A6 and SLC26A3. Hypocitraturia arises from less citrate excretion and heightened reabsorption. Citrate lowers the risk of stone formation, acidosis, and sodium ion levels, while certain disorders influence the concentration of citrate in urine. Hyperuricosuria arises from the malfunctioning of SLC22A12 and ABCG2 proteins. Alongside hereditary determinants, the intestinal microbiome, particularly Oxalobacter formigenes, regulates oxalate levels, and their decline increases the risk of oxalate stone formation. This metabolic disorder leads to urine supersaturation and facilitates the formation of crystals. New drugs, including RNA interference agents (nedosiran, lumasiran) and SGLT2 inhibitors (empagliflozin), present opportunities to tackle metabolic issues. Comprehending the mechanisms of metabolic dysregulation at the genetic level is crucial for formulating innovative therapeutics and minimizing recurrence. This article examines the molecular mechanisms underlying the formation of calcium oxalate stones due to metabolic disorders. Incorporated mutations in TRPV5/6, CLDN16, enzyme deficiencies, and dietary influences.

Keywords: Nephrolithiasis, supersaturation, genetic, hypercalciuria, hyperoxaluria, metabolic.

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INTRODUCTION

Nephrolithiasis, also known as urolithiasis, renal calculi, and kidney stones. It is a common urinary system disorder that is increasing in number among people worldwide [1, 2]. Males are more affected than females. Basically, the stone formation process includes supersaturation of urine, nucleation, growth & aggregation, then crystal retention within the urinary system. The imbalance between minerals in the urine and urine volume leads to a state of supersaturation [3]. In the nucleation process, free ions in a solution combine to form microscopic particles. Once nuclei form, other minerals attach to them, and these crystals can then clump together to form a hard & large stone [4]. Usually, small stone passes via the urinary system, but when they exceed 3 mm in diameter, they could result in ureteral obstruction, resulting in renal colic, post-renal azotemia, along with the hydronephrosis, hemorrhagic urine, pyuria, dysuria, vomiting, haematuria, fever, and nausea [5]. Renal colic is a serious, sporadic pain that radiates to the lower abdomen, groin, and flank [6]. If further stone size increases to around >5mm needed medical intervention like surgical removal is needed. Surgical extraction methods: There was a group of many modalities which were employed; they include ureteroscopy (URS), extracorporeal shock wave lithotripsy (ESWL), shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL), and, in a few extreme cases it employed the use of open surgery. Apart from stone size, these methods also depend on

location and patient health. These surgical methods are widely used, but they show some limitations that are used for large stones only, and may cause discomfort, pain, infection, bleeding, recurrence, and damage to organs [7, 8]. Stone can recur after some time of treatment & surgery, due to residual fragments or underlying metabolic factors. 50% of individuals will have a recurrence within 5-10 years after their first stone. Stone recurrence can be prevented by improving knowledge of the mechanics behind stone formation [9]. These stones are classified into five types, which include: calcium (calcium oxalate and calcium phosphate), cystine, uric acid, struvite (magnesium ammonium phosphate), and rare stones including drug-induced stone, xanthine, & brushite stones. CaOx and calcium phosphate (CaP) stones, either individually or in combination, are the most frequently observed, being radio-opaque on imaging. CaOx and urate stones are more prevalent in men, whereas struvite and carbapatite stones are more commonly found in women [10-12]. In India prevalence of nephrolithiasis reaches 12% and is more often in the northern parts (15-16%) [13]. This condition affects two million individuals each year, with a notable prevalence among men aged 31-40 years [14]. A Study of 300 kidney stone patients in southern India found that 76% were men, mostly aged 51-70, with a 60-90% recurrence risk [15]. Males face a lifetime risk of 12%, while females have a risk of 6%. The prognosis is concerning; estimates indicate a 30-40% chance of recurrence within five years [16]. The prevalence in populations is highly varied on many risk factors such as age, gender, diet practices, fluid consumption, climate, occupation, animal protein, socioeconomic status, geographic position, genetic predisposition, and metabolic diseases among many others [17, 18]. Further, patients with nephrolithiasis are under more risk of developing chronic kidney disease (CKD), end-stage renal disease (ESRD), and hypertension. Some medical conditions also increase the risk of stone formation. It has been determined remarkably that metabolic syndrome, diabetes, gout, and obesity all contribute significantly to the development of stones [19, 20]. Current medication and surgery manage symptoms but not the root causes of nephrolithiasis, for long-term solutions require deeper research & developing new therapies to treat nephrolithiasis.

MATERIAL AND METHODS

This systematic review was executed utilizing literature obtained from various electronic databases, such as PubMed, Scopus, and Web of Science. The employed search strategy amalgamated terminologies pertinent to nephrolithiasis, calcium oxalate, metabolic anomalies, genetic polymorphisms, microbiome interactions, and pathophysiological mechanisms. Emphasis was placed on systematic reviews, meta-analyses, and high-caliber narrative reviews published within the timeframe of 2000 to 2025, alongside the incorporation of significant primary research articles derived from both clinical and experimental investigations.

Calcium Oxalate stone:

Abnormalities in the urine's chemical composition affect the stones' chemical makeup, causing differences in the stones' size, form, and composition. The most common type is calcium-based stone, CaP and CaOx. They are present in the form of monohydrate (COM) and dihydrate (COD) [21]. Crystallographically, the CaOx group is divided into its hydration state: caoxite ($\text{CaC}_2\text{O}_4 \cdot 3\text{H}_2\text{O}$; COT), whewellite ($\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$; COM), weddellite ($\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$; COD), and anhydrous calcium oxalate (ACO) [22, 23]. The process of development of stones usually begins with the formation of Randall plaques, also known as calcium phosphates precipitates, which form on the papillary parts of the affected nephrons [24]. Such mineralized lesions also serve as a nucleation point to crystallization and consequent aggregation of calcium oxalate. The oxidative stress and the activation of inflammatory reactions, as well as an increase in immune processes, strengthen the morphogenesis of crystals of calcium oxalate in the renal tubules. Calcium stones are usually related to high oxalate intake, hypercalciuria, hypocitraturia, alkaline and dehydration [25]. For the measurement of COM & COD in stone, Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and micro focus X-ray computed tomography (CT) are used [26, 27].

Metabolic Disturbances:

Calcium Homeostasis Disruption:

Hypercalciuria includes overexpression of calcium in urine. In this condition amount of calcium in urine exceeded >250mg/day in women or >350mg/day in men, and in both >4mg/kg/day. Hypercalciuria is a multifactorial disorder resulting from a complex interactive process involving the intestines, kidneys, and bones, and is a major metabolic risk factor for calcium nephrolithiasis, osteopenia, and osteoporosis [28, 29]. In simple words increased amount of calcium due to disturbance of calcium absorption, reabsorption, and resorption, together called homeostasis disturbance [30, 31]. It is thought to be the primary cause of idiopathic calcium-based stones, accounting for approximately 85% of all cases of nephrolithiasis [32]. Blood calcium levels are regulated by three homeostatic regulatory mechanisms: physiologic,

physicochemical, and humoral, which likely mediate the maintenance of plasma calcium content [33]. Physiologic regulation relies on the interplay between the bone, kidney, and gut. Bones store >99% of the body's calcium in the form of hydroxyapatite crystals. The bone remodeling process involves osteoblasts (adding calcium) and osteoclasts (releasing calcium). Around 200-250mg of calcium goes into the extracellular fluid every day. This process is regulated by hormones (parathyroid hormone (PTH), calcitonin), body movements, and cytokines [34]. Dietary calcium is mostly absorbed in the duodenum and jejunum through two pathways transcellular and paracellular pathways. The transcellular active pathway depends on vitamin D. When calcium is low in the body, Transient Receptor Potential Vanilloid (TRPV6) proteins mediate calcium entry into the cell. In the cell, calcium binds with the cytosolic transporter calbindin-D9k. These cytosolic transporters transport calcium to PMCA1 located on basolateral members that proteins move calcium out into the bloodstream [35]. In the cytosol, inactive Vitamin D receptors (VDR) are present and bind with agonist Vitamin D (calcitriol); they become active and go inside the nucleus. In the nucleus, VDR forms a heterodimer complex with retinoid X receptor (RXR). This complex further binds with DNA-specific sequences called vitamin D response elements (VDREs) and regulates gene expression via protein making [36]. That regulates TRPV5/6 and calbindins expression and enhances calcium absorption. Paracellular transport works when higher calcium intake; calcium passes between cells without energy. This method depends on the concentration gradient. Kidney reabsorbs >98% of calcium by the proximal tubules, thick ascending limb, and distal convoluted tubules. The reabsorption is regulated same pathways, but the amounts of proteins vary. The TRPV5 protein is highly present in nephrons, and the TRPV6 highly expressed in the intestine. The TRPV5 reabsorbs calcium & transports into the cell. In the cell cytosolic transporter calbindin-D28k binds with calcium and reaches the pumps. Plasma Membrane Calcium ATPase 1b (PMCA1b) or NCX1 (Sodium-Calcium Exchanger 1). NCX1 removes calcium from the cell into the blood. In the TAL, calcium reabsorption occurs passively but depends on a certain protein, the sodium-potassium-2-chloride-cotransporter (NKCC2) creates a position charge, which facilitates passive diffusion of calcium through Claudine-19/16 s tight junction proteins. In hypercalcemic conditions calcium calcium-sensing receptors (CaSRs) are activated and suppress NKCC2 and Claudine activities [37, 38]. In the physicochemical regulation of calcium, ensure a stable level of ionized (free) calcium in the blood through a chemical mechanism. In blood, calcium is present in three forms: complex with anions, bound with albumin, and free form. This calcium balance is affected by blood pH (acidosis and alkalosis), calcium phosphate solubility, and hypoalbuminemia. Through these mechanisms, the body can promptly regulate calcium to support muscles and nerves [39]. Humoral and hormonal homeostasis of calcium is regulated via PTH, calcitriol, calcitonin, and other hormones. PTH is stimulated when blood calcium levels decrease. It increases osteoclast activities in bone, increases reabsorption of calcium in renal tubules, decreases reabsorption of phosphate, stimulates an enzyme that increases vitamin d active form (Calcitriol), and promotes absorption of calcium through the intestine. Overall, it raises blood calcium levels. Another hormone, calcitriol's active form of vitamin D, is synthesized in multiple steps involving the skin, liver, and kidney. In the liver, 25-hydroxylase converts cholecalciferol D3 into calcidiol, and in the kidney, 1 α -hydroxylase converts calcidiol into calcitriol. Another hormone, Fibroblast Growth Factor-23 (FGF-23), works when the calcitriol amount is high by decreasing calcitriol synthesis. FGF-23 maintains phosphate homeostasis and reduces calcitriol synthesis via activation of 24 α -hydroxylase (CYP24A1). They convert calcitriol into an inactive form. When blood calcium and phosphate levels decrease, calcitriol is triggered. Calcitriol increases the absorption of calcium or phosphate in the intestine, mildly increases reabsorption, and in bone works with PTH. Calcitonin is another hormone present in parafollicular cells. Hypercalciuria promotes calcitonin action through osteoclasts and reduces bone resorption [40]. Hypercalciuria or idiopathic hypercalciuria is divided into three subtypes: (A) Absorptive (higher absorption of calcium through the intestine), (B) Renal (reduced calcium reabsorption through the nephron), (C) Resorptive hypercalciuria (Reduction of calcium from bone) [41]

Intestinal hyperabsorption of calcium: VDR is a nuclear hormone receptor that regulates intestinal absorption of calcium. Some polymorphisms (FokI, BsmI) in VDR enhance sensitivity to bind calcitriol and calcitriol regulate the expression of TRPV6, calbindin-D9K, because of this, increasing absorption of calcium through the intestine [42, 43]. The PHT regulates via CaSR in response to calcium and also regulates Claudine-19/16. Mutations in the CaSR gene gain of functional mutation and a loss of functional mutation, leading to reduced/increased PTH amount or an imbalance in calcitriol secretion. Calcitriol further enhances calcium absorption, and PTH reduces calcium reabsorption in the kidney [44]. Another gene is Cytochrome P450 family 24 subfamily A member 1 (CYP24A1), mutations cause enhanced calcitriol activities that cause Idiopathic Infantile Hypercalcemia [45]. In the intestine, bacteria also

regulate calcium levels and antibiotics degrade bacteria because of increased calcium in the urine, increasing the risk of kidney stones [46, 47].

Renal calcium handling defects: Thick ascending limb (TAL) contains tight junctional proteins Claudin (CLDN16), CLDN19 and CLDN2. Recent genome-wide association studies (GWAS) add CLDN10. A mutation in CLDN10/16/19 disturbs calcium and magnesium reabsorption. These mutations cause familial hypomagnesemia with hypercalciuria (FHHNC) [48, 49]. TRPV5/6 also present in nephron metabolic acidosis and high sodium intake, causing downregulation of these proteins, because of reduced calcium in blood [50]. Another gene is Sodium-dependent phosphate transport protein (SLC34A1/A3), which regulates renal phosphate transporters. Mutations in these genes cause hypophosphatemia, stimulating calcitriol production. A study found SLC12A1 mutation, that mutations acts on Sodium-potassium-chloride transporter (NKCC2) [51, 52]. Fibroblast Growth Factor 23 (FGF23) is a bone-derived hormone; dysfunction in this factor causes genetic variants (KLOTHO, or GALNT3) and enhances calcitriol by suppressing renal 24-hydroxylase and contributes to hypercalciuria [53, 54]. In rare cases (Monogenic forms), Mutations in chloride voltage-gated channel 5 (CLCN5) disrupt proximal tubule calcium reabsorption, causing Dent's disease [55].

Increased bone resorption: Bone osteoclast activity also contributes to hypercalciuria. OPG (Osteoprotegerin), low amounts and high amounts of RANKL (Receptor Activator of NF- κ B Ligand) affect osteoclast activity, increasing calcium and bone breakdown [56, 57]. Parathyroid hormone-related protein (PTHrP) and PTH overactivity increase bone loss. This activity is seen in certain tumors and hyperparathyroidism [58]. The prevalence of inflammatory cytokines, especially the Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α), is observed in both chronic kidney disease and obesity, as they have a stimulating role on the osteoclast actions [59].

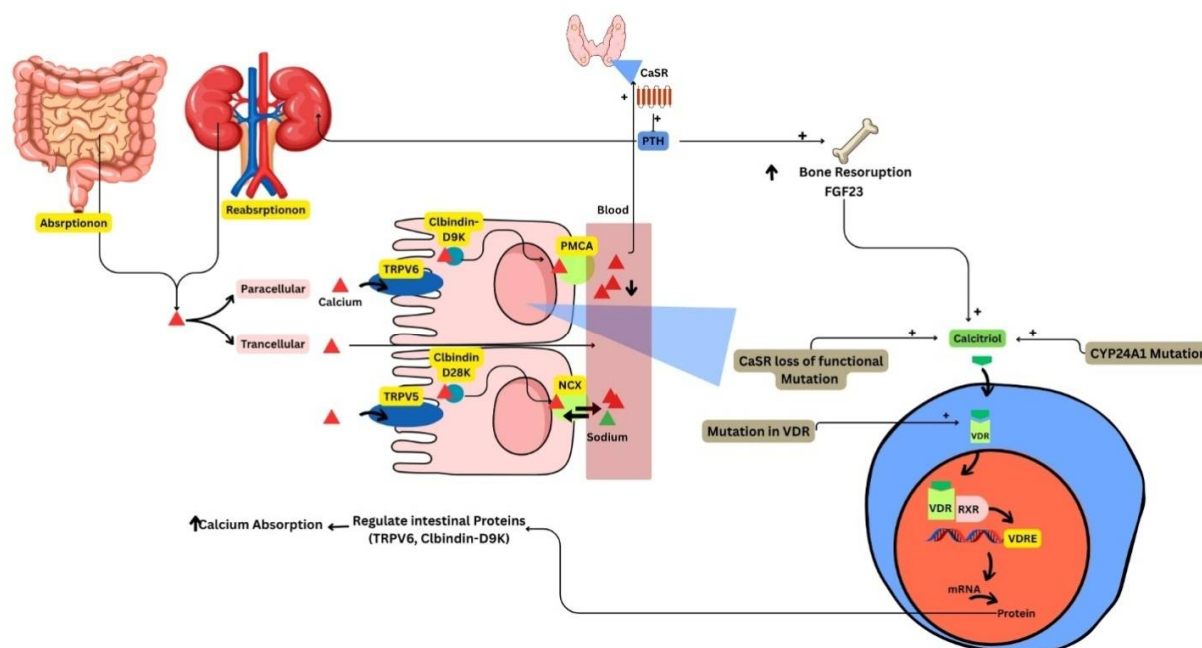


Figure 1: Low blood calcium promotes CaSR action, and CaSR regulates the PTH.

PTH does three major activities: intestinal calcium absorption, bone resorption, and renal reabsorption. PTH also promotes the synthesis of calcitriol, and calcitriol regulates the absorption and reabsorption. In the intestine and nephron, calcium is absorbed through the paracellular (small intersection) and transcellular pathways. In the paracellular pathway, calcium enters through TRPV5 and TRPV6 calcium channels, then calcium binds with calbindins (CB-D8k, CB-D9k), and after that, calcium is out through PMCA1b or NCX1. Lipid-soluble calcitriol enters into cell and binds with VDR located in the cell nucleus, dimerization with RXR (Retinoid X receptor & coactivators form a complex. This complex binds to specific DNA sequences, vitamin D response element (VDREs) on target genes, alters the gene expression, leading to various cellular effects like regulating intestinal or kidney proteins.

Oxalate Homeostasis Disruption:

Hyperoxaluria is characterized by an increased urinary oxalate excretion. In hyperoxaluria, oxalate concentration exceeds 40mg per 24hr. Oxalate in the body comes from two sources: endogenous (liver)

and exogenous (dietary). Liver, red blood cells, and ascorbic acid are endogenous sources of oxalate. Oxalate and its precursor are absorbed from the intestine. In the intestine, oxalate is absorbed through transcellular and paracellular pathways (between gaps) [60]. In the transcellular process, oxalate and chloride are absorbed through SLC26A3 and secreted by SLC26A6, or that transporter controls oxalate absorption in the intestine. The same transporter is present in the kidney. In nephrons, SLC26A6 antiport reabsorbs the oxalate and out-sulfate. In the intestine, bacteria decompose the oxalate and calcium bound with oxalate, forming an insoluble complex not absorbed via the intestine and is removed through the fecal route. Fatty acids decrease this calcium-oxalate binding and enhance absorption. The precursors of oxalate are converted liver into the direct precursor glyoxylate. Glyoxylate is converted into oxalate by lactate dehydrogenase (LDH) enzyme. In peroxisomes, glyoxalate and alanine convert into glycine or pyruvate via alanine glyoxalate aminotransferase (AGT). Glyoxalate/hydroxypyruvate reductase (GRHPR) converts cytosolic glyoxalate into glycolate. Glycolate is metabolised by Glycolate oxidase (GO) to form glyoxylate. In mitochondria, Hydroxy-2-oxoglutarate (HOG) is formed by hydroxyproline, which HOG transferred into glyoxylic acid and pyruvate by hydroxy-2-oxoglutarate aldolase (HOGA) enzyme [61, 62]. Hyperoxaluria is divided into two subtypes' primary hyperoxaluria (PH) and secondary hyperoxaluria. Primary is caused by metabolic error, while secondary is caused by dietary influence of oxalate, gastrointestinal disorder, or genetic [63]. Based on enzyme deficiency, PH is also categorised into three subtypes: types 1, 2, and 3. PH type I occurs when a defect in the enzyme (AGT) occurs, in type II, dysfunction of glyoxalate/hydroxypyruvate reductase (GRHPR) enzyme occurs, and in type III, 4-hydroxy-2-oxoglutarate aldolase (HOGA) enzyme defect occurs. These enzymes are related to specific genes (AGXT gene located on 2q37.3 chromosome, GRHPR gene located on chromosome 9p13.2, HOGA gene located on chromosome 10.q24.2). Mutations in these genes cause primary hyperoxaluria [63-65]. Secondary hyperoxaluria is related to three majorly 3 factors: (A) Oxalate-rich meals (such as spinach, cabbage, beets, almonds, or tea); vitamin C (>1000 mg/day); or calcium-deficient diets [66]. (B) Gastrointestinal disorders, chronic pancreatitis, pancreatic insufficiency, celiac disease, intestinal inflammation, or bariatric surgery [67]. (C) Excess urinary excretion, primarily caused by chronic kidney disease, exacerbates the problem due to its pro-inflammatory environment [68, 69]. Oxalate is degraded in the intestines, and this reduces its absorption and is heavily dependent on the intestinal bacterium *Oxalobacter formigenes* [70]. Disruptions to this bacterium due to antibiotics or low amounts in the gut may cause a weak digestive system may cause hyperoxaluria. The secondary hyperoxaluria is a kidney disease where the problem occurs due to pancreatic and gastrointestinal problems like pancreatectomy, orlistat use, Roux-en-Y gastric bypass, small bowel resection, Crohn's disease, Celiac disease, chronic pancreatitis, cystic fibrosis, and somatostatin-analog therapy. The conditions interfere with regular intestinal absorption of oxalate because of reasons such as fat malabsorption and calcium-oxalate imbalance. The condition is linked to a clinical outcome of a severe nature, oxalate nephropathy, which is a strong form of nephropathy and which may ultimately result in the (premature) death of the afflicted person [60]. Patients who experience oxalate nephropathy predisposing pancreatic exocrine insufficiency were determined to have a mutation of SPINK1 (Serine Peptidase Inhibitor, Kazal Type 1) and PRSS1 (Protease, Serine 1) genes [71]. The transport of oxalate is very dependent on the presence of transporters belonging to the SLC26 family, noted as SLC26A1, SLC26A3, and SLC26A6 transporters. The transporters assist in normalizing, synthesis, and intestinal and renal tubular absorption of oxalate. Malfunction and mutation in the transport system increase plasma oxalate level, which enhances the risk of calcium oxalate stone [72].

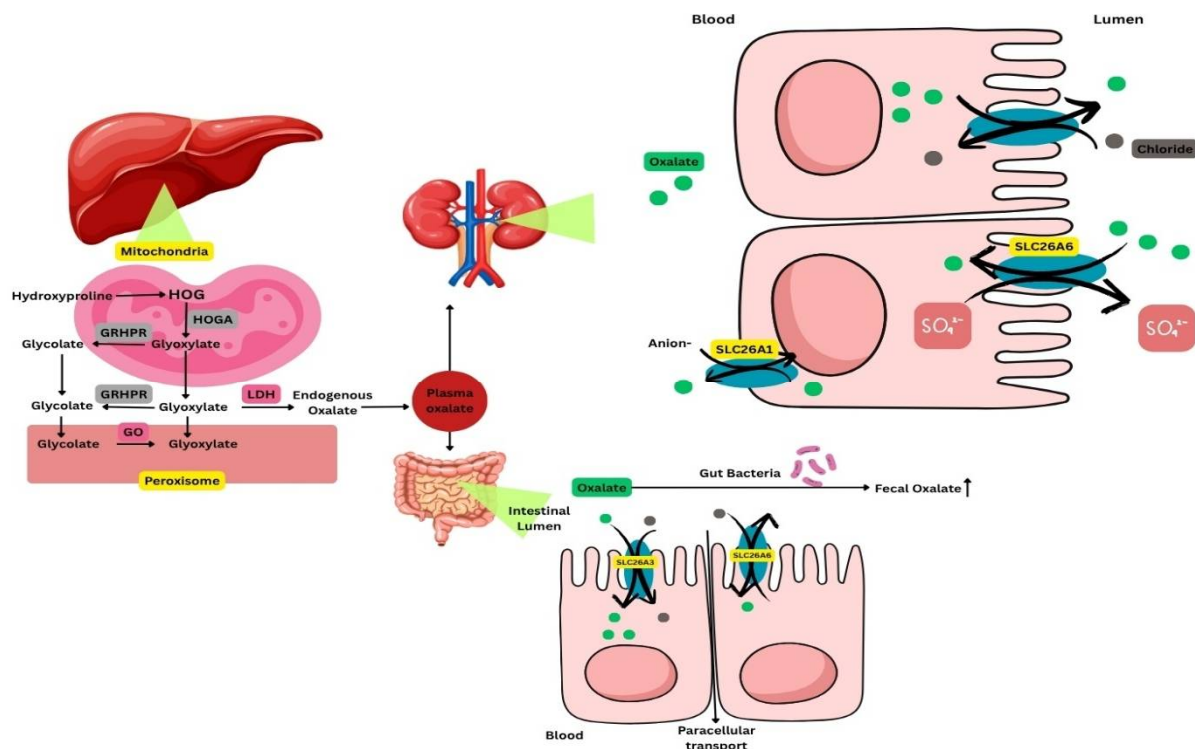


Figure 2: Oxalate comes from two sources: endogenous (internal) and exogenous (dietary) sources.

The liver converts oxalate precursor hydroxyproline into HOG, HOGA converts HOG into glyoxylate, a direct precursor of glyoxylate & it's further converted into oxalate via LDH enzyme. To reduce oxalate synthesis, various enzymes convert glyoxylate into alanine via AGT, glycolate via GRHPR, and glyoxylate via glycolate oxidase (GO) enzyme. Absence of GRHPR & AGT, glyoxylate produces oxalate in higher amounts, causing PH I, II. Endogenous process enhances plasma oxalate, further plasma oxalate goes to the kidney, in the kidney and intestine same protein channels work that reabsorb and secrete oxalate via proteins SLC26A6/A1/A3. In the intestine, oxalate is absorbed through SLC26A3 and secreted via SLC26A6. Bacteria influence the absorbance of oxalate, which promotes oxalate. SLC26A6 promotes the secretion of oxalate in the kidney.

Citrate Homeostasis Disruption:

About 20% to 60% of stone formers have hypocitraturia, which is typically described as discharge of urine citrate of less than 320 mg (1.67 mmol) per day [73]. Citrate, a naturally occurring inhibitor of the process of making stones, adheres to urine calcium, preventing its crystallization into stones. Low citrate levels increase calcium stone production, leading to renal calculi [74]. Citrate in the urine binds to magnesium and calcium, forming soluble compounds that help prevents calcium crystals from forming kidney stones. The proximal tubule of the kidney actively transports about 65-90 percent of the citrate with assistance of a protein by the sodium-dependent dicarboxylate transporter (NaDC1) [75, 76]. The citrate reabsorbed in the kidney is affected by pH, sodium ions, irritable colon syndrome (IBS), colitis, chronic diarrhoea, gastric bypass surgery, medications and some conditions such as a low potassium and metabolic acidosis which increase the citrate reabsorption and decrease the urinary citrate levels. Urine citrate is low which implies less calcium binding and increases the chances of forming kidney stones. Endothelin-1 also promotes citrate reabsorption by activating NaDC1 through endothelin B (ETB) receptors [77-79].

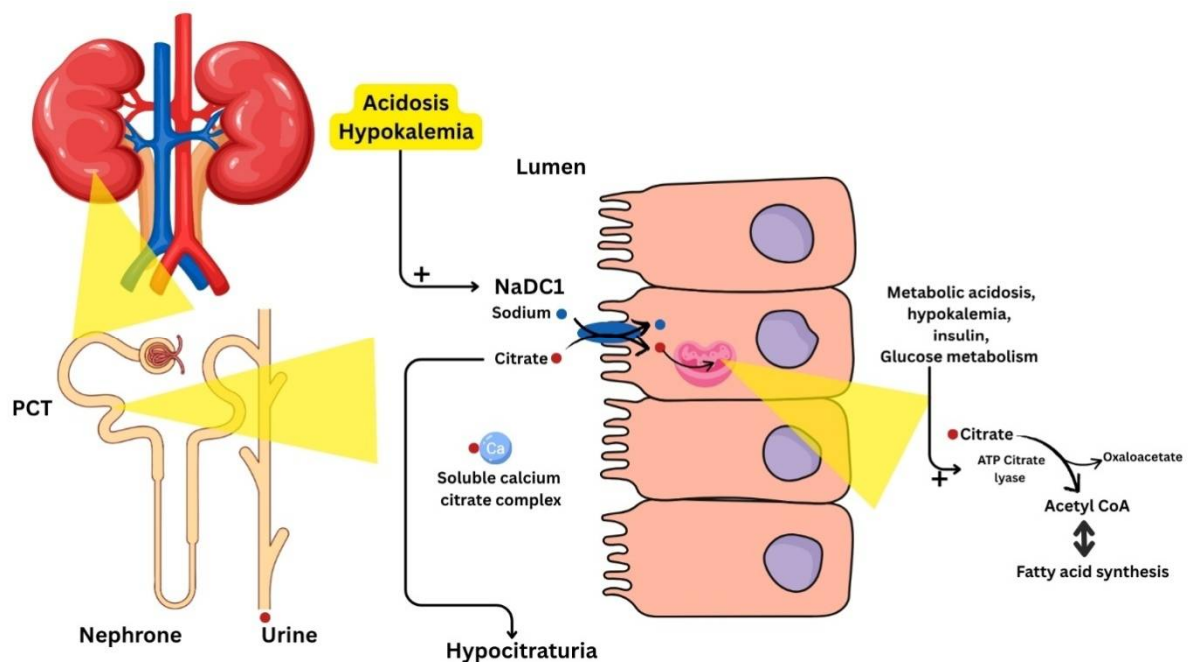


Figure 3: Citrate is filtered from the blood PCT. In lumen, calcium binds with citrate & forms a soluble complex;

this complex stops forming hard crystals. NaDC1 transports citrate and sodium into the kidney cells. Transporter becomes more active during Acidosis or hypokalemia conditions, transporting more citrate into the kidney cells and leaving less citrate in the urine. Citrate is broken down with the help of oxaloacetate into acetyl-CoA, & then converted into fatty acid.

Uric Acid Homeostasis Disruption:

Men excrete more than 800 mg of uric acid each day, while women excrete 750 mg, with an average threshold of greater than 600 mg/day, which is known as hyperuricosuria. It is generally brought on by myeloproliferative disorders and excessive purine intake [80, 81]. A balance between internal production, excretion through the gastrointestinal (GI), renal systems, and dietary purine consumption keeps the body's levels of uric acid (UA) stable [82]. Any imbalance concerning this axis can result in a change in serum UA levels. Both reabsorption and secretion of UA is controlled by various genes and proteins, and this process is more centered on the kidney and GI. SLC22A12 (encoding urate transporter 1/URAT1), SLC2A9 (encoding glucose transporter 9/GLUT9), and ATP-binding cassette sub-family G member 2 (ABCG2) (encoding breast cancer resistance protein/BCRP) are the key transporter genes involved in the processing of uric acid. In these genes (encoded transporter) disrupt renal tubular uric acid reabsorption, which increases its urinary excretion and decreases its serum urate levels. Certain variations, such as c.1419+1G>A and rs16890979 in SLC2A9 and (c.1245 1253del and c.1400C>T) in SLC22A12, have been identified as causative both in family-based and community-based studies, especially in certain ethnic groups [83, 84]. In recent studies that have done a genome-wide association, many coupled variants have been found to account in regions of the human genome that encode genes including ABCG2, SLC2A9, cut like homeobox 2 (CUX2), and glucokinase regulator (GCKR), which are linked to abnormalities in the transportation of uric acid, whether it is produced in excess or excreted less, in genome regions. Remarkably, the ABCG2 transporter is required in the excretion of uric acid through the kidney and bowel channels [85, 86].

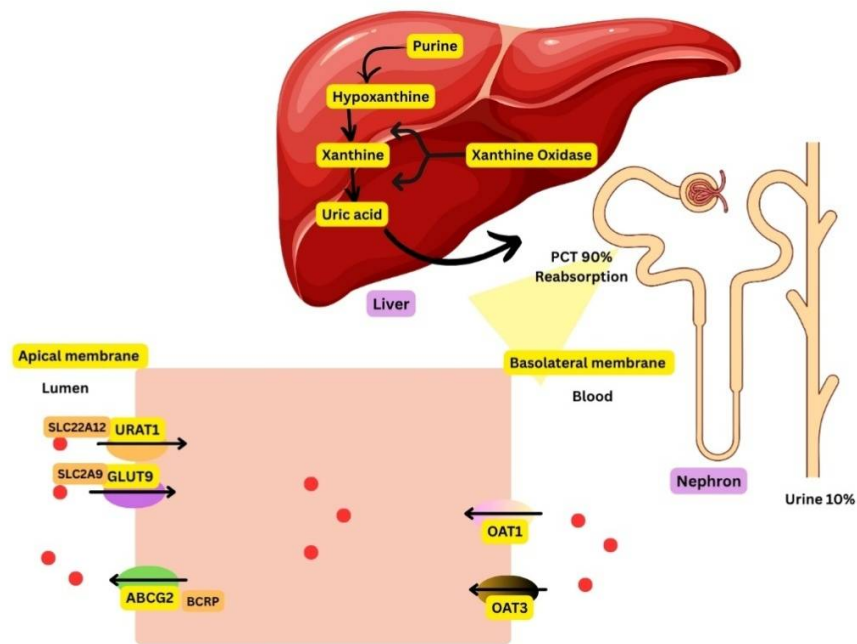


Figure 4: Formation of uric acid occurs in the liver, from purines to hypoxanthine, then converted to xanthine, and finally to uric acid with the help of the xanthine oxidase enzyme.

Then, uric acid enters the bloodstream and is filtered by the kidneys. In the kidney, PCT reabsorbs 90% of uric acid & the remaining 10% out from the body. In the Apical membrane of PCT, URAT1 that regulated by the SLC22A12 gene & GLUT9 regulated by the SLC2A9 gene, reabsorb uric acid from the tubular lumen into cells. Another protein, BCRP, which regulated by ABCG2, secretes uric acid from cells into the tubular lumen. On the basolateral membrane, Organic Anion Transporter 1/3 (OAT1/3) moves uric acid from blood into renal tubular cells.

Table 1: Genetics study of metabolic dysregulation in animals & human and their findings

Model/Species	Gene(s) / Pathway	Main Findings	Reference
Cat	Complement Receptor 2 (CR2), IKAROS Family Zinc Finger 3 (IKZF3), Leukocyte Selectin (L-selectin)	Those with CR2, IKZF3, L-selectin, which are some of the severely upregulated inflammatory genes in the CaOx stone-forming cat, may also differ in terms of the inflammatory responses to more general renal disease.	[87]
Mouse (Claudin-2 KO)	CLDN2 (Claudin-2)	Both hypercalciuria and nephrocalcinosis are linked to the deficiency of the Claudin-2. Studies have discovered some rare and common single-nucleotide variations in CLDN2 which are linked to a highly augmented lifetime risk of urolithiasis and a reduced level of claudin-2 in the kidney of the patients.	[88]
Rat (GHS model)	VDR, CaSR, TRPV6	An upregulation VDR expression in systemic tissues causes vitamin D to be more sensitive which is achieved concurrently by the upregulation of CaSR and TRPV6. This same sensitivity leads to the production of increased levels of calcium.	[89]
Rat (GHS model)	Osteoclast/Osteoblast genes	Decreased osteoblast & Increased osteoclast function decrease bone density and quality, due to increased VDR.	[90]
Human (Microbiome)	Oxalobacter formigenes	O. formigenes is the leading player of the oxalate degradation in the human gastrointestinal tract. The decrease in	[91]

		capacitation of oxalate-degrading pathways in inflammatory bowel disease (IBD) populations could even predispose them to nephrolithiasis.	
Mouse/Rat (PH1 model)	<i>Oxalobacter formigenes</i>	The study found that oral use of <i>O. formigenes</i> can maintain renal health despite increased oxalate burden, possibly due to a direct metabolic intervention in the gastrointestinal tract. This suggests that oral <i>O. formigenes</i> intake may impact systemic oxalate metabolism, not just urine oxalate levels.	[91, 92]
Human	NaDC-1	The rs11567842 polymorphism in the gene of NaDC-1 is not related to hypocitraturia; the mutation rates in hypocitraturic and normol citraturic patients cannot be significantly different.	[93]
Human	TRPV5	The renal calcium-wasting hypercalciuria is a rare disease that is carried by biallelic TRPV5 mutation as an autosomal recessive trait. Physiologically, it interferes with the monovalent cation-specific calcium channel of the late distal convoluted tubule and as a result, the negative reabsorption of the calcium ions is affected.	[94]
Human	Polygenic (multiple genes: CLDN2, TRPV5, CaSR, VDR, SLC34A3, CLDN16)	Heritability is high, attributed to single-gene defects and multifactorial polygenic factors, affecting calcium transporting proteins and vitamin D metabolism.	[95-97]
Human PH (I, II, III)	AGXT, GRHPR, HOGA1	Mutations in AGXT, GRHPR, and HOGA1 cause PH1, PH2, and PH3, with varying severity and severity within families, and new variants found in diverse populations.	[98, 99]

Future perspective and management strategies for metabolic disturbances:

Metabolic disorders such as hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria. New therapy aims at addressing these problems with the help of changes in the diet and certain medications. In hypercalciuria, reduction in the consumption of sodium and animal proteins (but not calcium) will be accompanied by the use of thiazide diuretics (hydrochlorothiazide, chlorthalidone) [100]. Hyperoxaluria is addressed by restricting the intake of oxalate in the diet, dietary calcium supplementation, and pyridoxine (B6) in hereditary disease. Hypocitraturia is initially managed with potassium citrate and increased fruit and vegetable consumption. Allopurinol effectively treats hyperuricosuria, especially with reduced animal protein and purine-rich foods [101]. Small stones do not require invasive procedures; they are treated by medication and lifestyle modification. Depending on the stone types, treatment varies. Medication involves pain relief, thiazides, potassium citrate, allopurinol, Acetohydroxamic acid (AHA), calcium channel blockers, alpha blockers, and antibiotics are used [102, 103]. Lifestyle modification involves hydration and dietary control of sodium, oxalate, and proteins. The latest therapies and upcoming therapies are treating metabolic dysregulation at the genetic level.

Table 2: Latest therapies, upcoming therapies and their current status.

Therapies	Mechanism	Status	References
Empagliflozin	Reduce kidney glucose reabsorption	Food and Drug Administration (FDA) (2023)	[104, 105]
Tenapanor	Sodium/Hydrogen Exchanger 3 (NHE3) inhibitor, stop intestine phosphate absorption	FDA (2023)	[106]
Nedosiran	Target lactate dehydrogenase, RNAi therapy, PH1 treatment	FDA (2023)	[107]
Lumasiran	Glycolate oxidase inhibitor & reduce oxalate	Phase III clinical research	[108]

Future direction of stone management is moving towards personalized therapies. It's included genetic test to choose best dose and drugs for each patient. Scientist made new therapies to target specific

substance & genes in the body. lactate dehydrogenase, glycolate oxidase, osteopontin these substance and enzymes targeting for new therapeutics development [2]. Latest research focused on reduce medication regularly and side effects. These improvements object to make nephrolithiasis treatment more effective and easier to follow [109].

CONCLUSION

CaOx nephrolithiasis is a thorny disease influenced by environmental, genetic, and metabolic factors. Essential causes are hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria, whose molecular processes occur differently, including the change in calcium grid and oxalate transportation, hormonal disturbance, and the mutation of genes. In addition to the stone's formation, the disruption of the microbiota in the gut, the decline in urine inhibitors such as citrate, and the dysfunction of renal transporters. Genetic and microbial pathogenesis of stone has been extended with the latest data on human and animal models. However, existing treatments mainly control symptoms but not the origins of the disease that lie in metabolism. Thus, the importance of integrative strategies targeting genetic, metabolic, and bacterial control will be vital in preventing the recurrence and devising long-term approaches to the problem of nephrolithiasis.

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