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Catalytic power of oxalate in the development of renal calculi: Review

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Abstract
Renal calculi, which are common urological problems with frequent recurrences, have been effectively managed with the development of minimally invasive procedures. Although contemporary stone treatment procedures have reached a level of maturity, their main focus is on dealing with stones that already exist, and they face challenges in effectively preventing the occurrence and reappearance of stones. This underscores the necessity of prioritizing prevention following therapy. Renal calculi are predominantly composed of calcium oxalate, accounting for more than 80% of cases. Although there is considerable study on urinary calcium metabolism, there is a significant lack of understanding on the specific role of oxalate. Oxalate and calcium are both essential components of calcium oxalate stones, and abnormalities in oxalate metabolism and excretion are significant factors in their formation. This review examines the relationship between kidney stones and the metabolism of oxalate, with a specific focus on the processes of oxalate absorption, metabolism, and excretion. This study examines the vital function of SLC26A6 in the removal of oxalate and investigates the regulatory mechanisms that govern SLC26A6 in the transport of oxalate. This review offers innovative perspectives on the mechanisms of kidney stones by specifically focusing on the oxalate viewpoint. This study improves our comprehension of the function of oxalate and provides remedies to decrease the frequency and reappearance of kidney stones.

Keywords: Renal calculi, oxalate, gut microbiome, SLC26A6, prevalence

Introduction
Renal calculi are a prevalent urological issue, with a global increase in prevalence and incidence. A national survey found a 6.4% prevalence, affecting about 1 in 17 adults, with higher rates among men (6.5%) than women (5.1%) [1]. In the United States, the prevalence is consistently rising [2], and stones frequently recur post-treatment, with an estimated recurrence rate of 50% [3]. Studies by O Kamihira *et al*. indicate recurrence rates of 6.7%, 28.0%, and 41.8% after 1, 3, and 5 years, and in children, rates of 26%, 35%, 41%, and 46% after 5, 10, 15, and 20 years, respectively [4, 5]. Renal calculi formation is associated with a higher risk of diseases like hypertension, chronic kidney disease, and end-stage renal disease, posing a substantial annual health burden [6, 7].
The key steps in the formation of renal calculi include urine supersaturation, nucleation, crystallization, growth, and aggregation [8]. Nucleation and crystallization, fundamental chemical processes, occur regardless of the stone production method. Randall's theory, widely acknowledged, centers on the formation of calcium phosphate crystals in the renal interstitium. Crystals in the shape of plaques develop below the epithelial layer on the basement membrane of the Henle loop. Approximately 75% of calcium oxalate stones are associated with Randall's plaque, a condition characterized by the gradual buildup of minerals and their infiltration into the epithelium, ultimately leading to stone formation.

Oxalate and Renal Calculi
Oxalate plays a vital role in the production of kidney stones, specifically calcium oxalate stones, which make up more than 80% of these stones [10]. The production of these stones is driven by the supersaturation of urine calcium oxalate, which is caused by key risk factors such as hypercalciuria and hyperoxaluria. Studies extensively investigate the formation of stones in relation to urinary calcium metabolism.

However, It is crucial to emphasize that the role of oxalate, which is a crucial raw material, is equally or even more significant than that of calcium [12]. The urine oxalate content is crucial, as even small changes can have a major effect on the development of calcium oxalate crystals [12-14]. Hyperoxaluria not only encourages the formation of calcium oxalate crystals, but also harms the cells lining the renal tubules, making it easier for the crystals to stick to them due to oxidative stress. Subsequent immune inflammatory responses contribute to the further enhancement of Randall plaque development [15]. Research suggests that hyperoxaluria causes a transformation of renal tubular epithelial cells into osteoblast morphologies, which contributes to the production of Randall plaque and kidney stones [16].

Source of oxalate

The sources of oxalate are categorized into external and endogenous origins, as seen in Figure 1. Exogenous sources refer to the absorption of oxalate from the diet by the intestine, which accounts for 20-40% of the oxalate found in the blood. The liver, red blood cells, and ascorbic acid are endogenous sources that generate oxalate via metabolic processes [17]. Overproduction of oxalate results in the development of hyperoxaluria and the creation of oxalate stones. People who have inherited glyoxylate diseases release too much oxalate into the urine, which leads to primary hyperoxaluria. Increased oxalate consumption, a diet low in calcium, impaired fat absorption, and changes in the composition of gut bacteria are some of the causes of secondary hyperoxaluria [18].

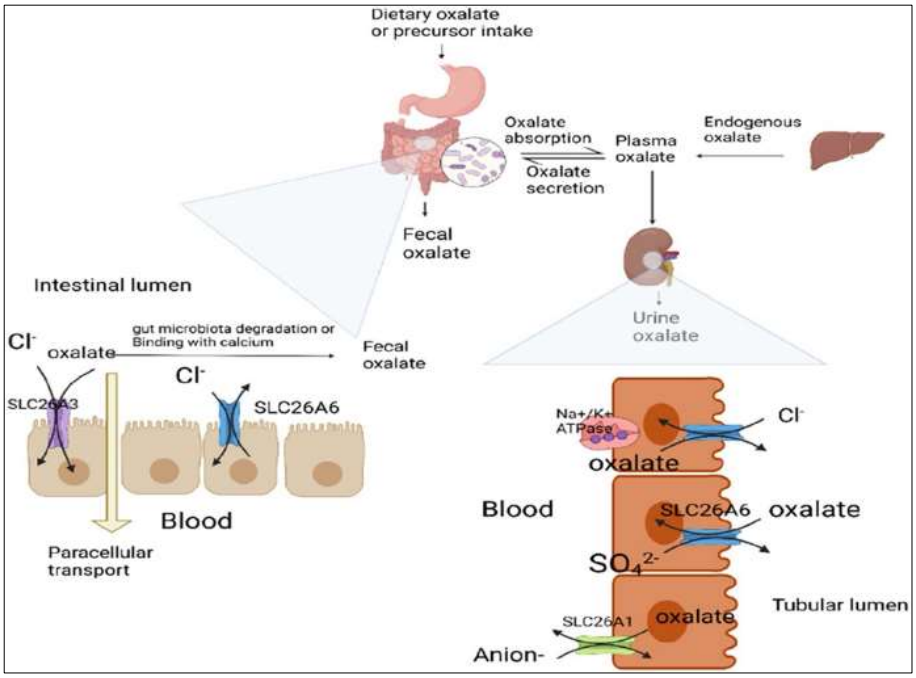

Fig 1: Illustrates the absorption mechanism of oxalate in the intestine and kidney

Endogenous sources of oxalate and primary hyperoxaluria

Approximately 60-80% of plasma oxalate is produced endogenously by hepatic metabolism [19]. In the liver, lactate dehydrogenase (LDH) converts glyoxylate into oxalate as part of a metabolic process. The enzymes Alanine-glyoxylate aminotransferase (AGT) and glyoxylate reductase-hydroxypyruvate reductase (GRHPR) reduce the concentrations of naturally present oxalate by converting glyoxylate into glycine and metabolizing glyoxylates, respectively. The enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA) aids in the hydroxyproline metabolism process, as depicted in Figure 2. Insufficient enzyme levels lead to an excess of naturally occurring oxalate, resulting in primary hyperoxaluria. The most severe form, Type 1, can be further classified into three subtypes: Type 1 with a genetic deficiency of AGT, Type 2 with a genetic deficiency of GRHPR, and Type 3 with a genetic deficiency of HOGA. Primary hyperoxaluria results in the accumulation of oxalate, the formation of renal calculi, and renal impairment, ultimately culminating in end-stage renal failure [18].

Figure 2: Illustrates the hepatic metabolic route of oxalate. Metabolic conversions occur within hepatocytes, where different oxalate precursors are transformed to generate the immediate precursor glyoxylate. Subsequently, lactate dehydrogenase (LDH) converts glyoxylate into oxalate.

Exogenous sources of oxalate

Around 20-40% of the oxalate found in the plasma comes from the food we eat and is taken in by the intestine. Although exogenous oxalate only makes up a small part of the total oxalate in the blood, its levels can be influenced by different circumstances, making it extremely variable and easily changed by individuals. Managing exogenous oxalate offers a pragmatic strategy to proactively avoid the development of kidney stones. Experiments conducted on mice with hyperoxaluria, who were given a diet without oxalate, demonstrated a notable enhancement in hyperoxaluria. This confirms that a considerable amount of urinary oxalates originate from the intestines [19]. Therefore, it is essential to understand the process by which oxalate is absorbed in the intestine and to determine the elements that impact its absorption.

Absorption mechanism of oxalate in the intestine

The mechanism of oxalate absorption in the intestine, whether paracellular, transcellular, or a combination, remains inconclusive. Knauf *et al.* [21] observed mouse intestines, suggesting passive paracellular absorption of oxalate, dependent on the balance with SLC26A6-mediated oxalate secretion. In contrast, Robert W. Freel *et al.* [22] found varied oxalate fluxes in WT and DRA knockout mice, proposing SLC26A3 mediates oxalate absorption across cellular pathways. Discrepancies were attributed to technical differences, with Whittamore *et al.* [23] indicating a potential involvement of both paracellular and transcellular pathways in oxalate absorption.

Factors affecting intestinal absorption of oxalate

Various variables affect the absorption of oxalate in the intestines, including the action of intestinal microorganisms, the type of oxalate, and the process of absorbing fat in the intestines. A diet deficient in calcium is seen as a contributing factor for the production of oxalate stones. This is due to the presence of calcium in the intestines can react with oxalate to form calcium oxalate, which is insoluble and difficult to absorb. Consequently, it is eliminated through defecation. Inadequate dietary calcium results in reduced bonding of oxalate to other substances, facilitating its absorption and causing elevated levels of oxalate in the bloodstream (Hyperoxalemia) [24-26]. A recent case study investigated the impact of a diet lacking calcium on hyperoxaluria, a medical disease defined by elevated levels of oxalate in the urine. The study revealed that reintroducing calcium into the diet resulted in a substantial reduction in the concentration of oxalate in the urine. This underscores the need of consuming calcium to avoid the development of calcium oxalate kidney stones [27].

In addition, insufficient absorption of fats or a diet high in fats can lead to increased levels of unbound fatty acids. These fatty acids can then bind with calcium from the diet, resulting in an increase in the amount of unbound oxalate and its absorption. Fatty acids additionally increase the permeability of the nearby mucosa, facilitating the absorption of oxalate [28, 29]. The occurrence of hyperoxaluria and stone formation significantly increases after Roux-en-Y gastric bypass and malabsorption bariatric surgery, mainly due to impaired fat absorption [31-34]. Conditions marked by inadequate fat absorption, such as Crohn's disease [35, 36], biliary tract disease [30], pancreatic disease [37], and short bowel syndrome [38], frequently display hyperoxaluria. When people have difficulty absorbing fat, taking fat-soluble vitamins as supplements is found to be associated with a decrease in the amount of oxalate excreted in the urine [39].

Intestinal microbes and oxalate metabolism

Preventing calcium oxalate stones may be achieved by enhancing intestinal oxalate degradation, addressing the origin of hyperoxaluria. The lack of an inherent oxalate degradation pathway in the human body necessitates the exogenous acquisition of oxalate-degrading enzymes. Oxalate-degrading bacteria, including "specialist oxalotrophs" like Oxalobacter formigenes and "generalist oxalotrophs" Bacteria such as Bifidobacterium animalis, Lactobacillus acidophilus, and Lactobacillus gasseri possess frc and oxc genes within the human intestine. Benjamin K. Canales *et al.* [51] showed that model rats colonized with O. formigenes experienced a 74% drop in the amount of oxalate excreted in their urine. Similarly, Bernd Hoppe *et al.* [59] found that patients who took O. formigenes oral preparations experienced a 19% reduction in urinary oxalate after 24 hours. Intestinal colonization by bacteria that can break down oxalate is a potentially effective approach to decrease the absorption of oxalate and avoid the formation of oxalate stones [40-64].

Structure and physiological function of SLC26A6

The solute-linked carrier 26 gene family 6 protein (SLC26A6) acts as a versatile anion exchanger, displaying the broadest range of transport capabilities within the SLC26A family. It facilitates the transportation of diverse anions [76]. SLC26A6 is a transmembrane secondary transporter composed of 759 amino acids. The protein possesses a domain responsible for inserting into the membrane, consisting of 14 α-helices of different lengths. The helices are organized into two structurally analogous segments. The structure of each area is composed of seven transmembrane segments, which are organized in two inverted repetitions [77]. The C-terminus harbors a STAS domain, which exerts a pivotal function in intracellular transportation and protein-protein interactions. Eliminating this domain impedes the transport of substrates within the membrane region [78, 79] Furthermore, the C-terminus has a common PDZ interaction motif, similar to that seen in the cystic fibrosis transmembrane conductance regulator (CFTR). This motif facilitates essential protein-protein interactions that are required for the assembly of multiprotein complexes [80]. SLC26A6 is highly prevalent in several human tissues and serves as a flexible transporter for a wide range of anions. It enables the transport of anions, including chloride/hydrogen carbonate, chloride/formic acid, chloride/oxalate, chloride/nitrate, sulfate/oxalate, and chloride/hydroxide. SLC26A6 plays a crucial role in preserving ion equilibrium and acid-base homeostasis. The presence of any dysfunction in SLC26A6 is highly correlated with a variety of diseases. It is glycosylation that makes SLC26A6's transportation function possible, and research has shown that N-glycosylation is a key part of the folding, transport, and function of many membrane proteins [83]. Glycosylation on promoters 167 and 172 is essential for the oxalate transport pathway. The activity of oxalate transport is significantly reduced by removing glycosylation [84]. The kidneys and gut have SLC26A6 that doesn't work right, which is linked to high levels of hyperoxalate in the blood and urine and the formation of renal calcium oxalate stones [85].

Oxalate excretion in the renal and stone formation

The primary route for the excretion of oxalate is via the renal system, predominantly through glomerular filtration [86]. The secretion in the renal tubules also affects the excretion of oxalate [87, 88]. In individuals without previous medical conditions, oxalate is efficiently eliminated by the glomeruli, and its excretion in the renal tubules is regulated by SLC26A6 [89]. Therefore, alterations in SLC26A6 expression could impact the release of oxalate, and the control of SLC26A6 expression has the ability to influence the secretion of oxalate in the proximal tubules. The SLC26A6 protein, which is found on the inner surface of the proximal tubule, helps move oxalate from cells to urine by exchanging Cl- ions with it. This helps the body get rid of

oxalate. It can also help move oxalate from the urine into the cell through a process called SO_4^{2-}/oxalate exchange, which is a way for oxalate to be reabsorbed [17]. Perfusion studies have shown that in rats, the S1 and S2 sections of the proximal tubule take in oxalate, while the S3 section releases oxalate [87, 90]. When the kidneys don't properly express SLC26A6, it can cause problems with the removal of oxalate. This can lead to high levels of oxalate in the urine and the formation of oxalate stones.

Oxalate excretion in the intestine and stone formation

The digestive tract serves as an auxiliary route for the excretion of oxalate by the kidneys, playing a vital function in restricting the overall uptake of oxalate by the intestines. Which means that this restriction limits how much oxalate the kidneys can get rid of. This lowers the amount of oxalate in the urine and stops oxalate stones from forming. The mediation of oxalate secretion in the stomach relies on SLC26A6 [94, 95]. Research conducted by Zhirong Jiang *et al*. discovered a notable occurrence of hyperoxalemia, hyperoxaluria, and oxalate stones in mice that lacked the SLC26A6 gene [94]. The suggested mechanism says that when mice don't have the SLC26A6 gene, there is less oxalate released in the stomach by SLC26A6. This means that more oxalate is absorbed in the colon. Due to the high amount of oxalate in the blood, the body excretes more of it through urine. This is called hyperoxaluria and it can lead to the formation of oxalate stones. Similar results were seen by Robert W. Freel *et al*., who found that oxalate production changed into oxalate absorption in the ileum of SLC26A6 KO mice compared to wild-type (WT) mice. The urinary excretion of oxalate in mice without the SLC26A6 gene was found to be four times higher than in animals with the wild-type (WT) gene. In a study [95], it was found that giving WT mice an injection of the inhibitor DIDS, which targets the mouse anion transporter SLC26A6, changed the ileum. Particularly, the ileum shifted from secreting oxalate to absorbing it. After more research, these results were confirmed, showing a link between problems in the SLC26A6 gene and the development of urolithiasis [96, 97]. The rat model of chronic renal failure showed that SLC26A6-controlled oxalate secretion from the intestines is important for lowering the body's overall oxalate levels [98]. Oxalate gets into the distal colon of mice through a different network than SLC26A6. This network may include other transporters that haven't been found yet [99]. When the kidneys have more SLC26A6, they get rid of more oxalate in the urine, which makes kidney stones more likely to form. In contrast, overexpression of SLC26A6 in the intestine leads to increased production of oxalate in the intestines and decreased excretion of oxalate in urine. This protects against the formation of stones. Therefore, SLC26A6 is anticipated to be an extremely advantageous target for the treatment and prevention of stone formation. Modulating the expression of SLC26A6 by either up-regulating or down regulating it has the potential to inhibit the production of renal calculi.

SLC26A6 gene mutation and oxalate stones

SLC26A6 is crucial in the prevention of kidney stones as it controls the overall absorption of oxalates in the intestines. Dysfunctions and genetic alterations in the human SLC26A6 gene can result in hyperoxaluria and the development of renal calculi. Multiple studies have examined the influence of SLC26A6 genetic variations on the formation of kidney stones in humans [100-104].

Six missense mutations in the SLC26A6 gene were found in both the case and control groups during the original research. The mutation C.616G > A (p.Val206 Met) was the most prevalent (11%), however, it did not have a significant impact on plasma or urine oxalate levels in the population [100]. A separate investigation examined the correlation between the SLC26A6 gene 206 M polymorphism and the susceptibility to renal calculi in individuals diagnosed with primary hyperparathyroidism (PHPT). The results showed no association between the SLC26A6 gene 206M polymorphism and renal calculi in patients with primary hyperparathyroidism (PHPT) [87].

Xiuli Lu *et al*. performed computational screening to find non-homologous single nucleotide polymorphisms (nsSNPs) linked to kidney stones in the SLC26A6 gene. The study discovered a non-synonymous single nucleotide polymorphism (nsSNP) called rs184187143 as a potentially disease-related variation in the SLC26A6 gene. Individuals who carry the C allele had a 6.1 times increased chance of developing kidney stones compared to those who have the G allele [88]. Liana and colleagues discovered two new variations in the STAS domain of the SLC26A6 gene. The alterations caused a disruption in the control of NADC-1-mediated citrate transport by decreasing the connection between the STAS domain of SLC26A6 and NADC-1. This led to the development of hypocitraturia and the formation of calcium oxalate kidney stones [89].

In a recent study conducted by Nicolas Cornière *et al*., a rare heterozygous missense mutation (c.1519C > T/p.R507W) in the SLC26A6 gene was discovered in a patient with calcium oxalate nephrolithiasis and severe hyperoxaluria. Transfecting the R507W mutation into OKP cells resulted in reduced expression of SLC26A6 and a notable decline in oxalate transport activity. The findings strongly indicate that the p. R507W mutation has an impact on both the expression and transport function of SLC26A6 [90].

Conclusion

Given the prevalent occurrence and recurrence of renal calculi, urologists tend to prioritize treatment over preventive measures. However, the paramount importance of prevention necessitates a shift in focus for future research toward understanding the etiology and pathogenesis of renal calculi. Calcium oxalate stones, a predominant type, can be effectively mitigated through targeted interventions addressing the source and excretion of oxalate. Intestinal bacteria responsible for oxalate degradation play a crucial role in limiting oxalate absorption, contingent on the intricate composition of the entire intestinal flora. The development of bacterial therapies for kidney stone prevention should thus consider the complexity of the entire intestinal microbiome.

SLC26A6 emerges as a key player in oxalate excretion, presenting a potential target for both the prevention and treatment of renal calculi. Its expression in the intestine facilitates oxalate excretion, thereby reducing urinary oxalate and providing a protective effect against renal calculi. Conversely, its expression in the kidney promotes oxalate excretion, leading to increased urinary oxalate and the promotion of renal calculi formation. Future research endeavors should validate the practicality of selectively up-regulating or down-regulating the SLC26A6 gene for

preventing and treating oxalate stones. Our current understanding of stone etiology and pathogenesis remains limited, underscoring the need for further research to deepen our insights in this critical domain.

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