Recent advances on the mechanisms of kidney stone formation (Review)

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Abstract. Kidney stone disease is one of the oldest diseases known to medicine; however, the mechanisms of stone formation and development remain largely unclear. Over the past decades, a variety of theories and strategies have been developed and utilized in the surgical management of kidney stones, as a result of recent technological advances. Observations from the authors and other research groups suggest that there are five entirely different main mechanisms for kidney stone formation. Urinary supersaturation and crystallization are the driving force for intrarenal crystal precipitation. Randall's plaques are recognized as the origin of calcium oxalate stone formation. Sex hormones may be key players in the development of nephrolithiasis and may thus be potential targets for new drugs to suppress kidney stone formation. The microbiome, including urease-producing bacteria, nanobacteria and intestinal microbiota, is likely to have a profound effect on urological health, both positive and negative, owing to its metabolic output and other contributions. Lastly, the immune response, and particularly macrophage differentiation, play crucial roles in renal calcium oxalate crystal formation. In the present study, the current knowledge for each of these five aspects of kidney stone formation is reviewed. This knowledge may be used to explore novel research opportunities and improve the understanding of the initiation and development of kidney stones for urologists, nephrologists and primary care.

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1. Introduction

Kidney stone disease, also known as nephrolithiasis or urolithiasis, is one of the oldest diseases known to medicine. It is estimated that 1-15% individuals suffer from kidney stone formation at some point during their lifetime, and the prevalence and incidence of kidney stone is reported to be increasing worldwide (1,2). A recent study concluded that the prevalence of kidney stones was 5.8% among Chinese adults (6.5% in men and 5.1% in women), with about 1 in 17 adults currently affected (3). Without proper treatment, kidney stones can cause the blockage of the ureter, blood in the urine, frequent urinary tract infections, vomiting or painful urination, culminating in the permanent functional damage of the kidneys (4). The worldwide prevalence of urolithiasis has increased over the past decades. Urolithiasis is often a recurrent and lifelong disease with a recurrence rate of 50% within 5-10 years and 75% within 20 years (5). Some studies have indicated that an increase in kidney stone occurrence is expected, due to multiple environmental factors, including changes in lifestyle and dietary habits, as well as global warming (1,4,6). However, precise factors responsible for the upward prevalence and recurrence of urolithiasis have not been identified yet. Due to its high prevalence in adults of working age, kidney stone disease has a substantial impact on the individual and society, and has become a public health issue, particularly in populations residing in regions with a hot and dry climate (7,8).

There are mainly five types of kidney stones according to the mineralogical composition, including calcium oxalate (CaOx; 65.9%), carbapatite (15.6%), urate (12.4%), struvite [(magnesium ammonium phosphate), 2.7%], brushite (1.7%) (9,10). Kidney stones can be broadly categorized into calcareous (calcium containing) stones and non-calcareous

stones. The most common types of human kidney stones are CaOx and calcium phosphate (CaP), either alone or combined, which are calcareous and radio-opaque stones (9,11). Kidney stones form at a foundation of CaP termed Randall's plaques (RPs), which begins at the basement membranes of thin limbs of the loop of Henle on the renal papillary surface (12). CaOx and urate stones exhibit a higher occurrence in males, whereas higher percentages of carbapatite and struvite stones are observed in females than in males (10,13). However, the role of sex differences in the pathophysiological mechanisms of urinary stone disease are not yet fully understood.

Regardless of the type, kidney stone formation is a complex and multistep process that includes urinary supersaturation, crystal nucleation, growth and aggregation (11,14). Kidney stone formation is associated with systemic disorders, including diabetes (15), obesity, cardiovascular diseases, hypertension and metabolic syndrome (16,17). Conversely, nephrolithiasis patients [also known as kidney stone formers (KSF)] are at a risk of developing hypertension (18), chronic kidney disease (CKD) (19) and progression to end-stage renal disease (ESRD) (20,21). Multiple promoting factors and inhibitors have been reported to play critical roles in kidney stone formation. For example, hyperoxaluria, hyperuricosuria and phosphaturia are common promoting factors linked to kidney stone formation (22,23); inter-α-inhibitor (IαI), a member of the protease inhibitor family, has been shown to inhibit CaOx crystallization *in vitro* (24).

Although details of human stone formation have accumulated, kidney stone formation and growth mechanisms are far from being clarified. The present review provides an update on the mechanisms of kidney stone formation, in order to improve the understanding of kidney stones for urologists, nephrologists and primary care givers.

2. Physicochemical mechanism of kidney stone formation

Urinary supersaturation and crystallization are the driving force for intrarenal crystal precipitation and is mainly caused by inherited or acquired diseases associated with renal function impairment. Additionally, urinary supersaturation and crystallization are influenced by urine pH and specific concentrations of substance excess, including CaOx, CaP, uric acids and urates, struvite, amino acids (cysteine), purines (2,8-dihydroxyadenine and xanthine) and drugs (e.g., atazanavir, sulfamethoxazole, amoxicillin, ceftriaxone) (25,26). Additionally, crystal formation and development are influenced by multiple modulator molecules, which are known as receptors, promoters and inhibitors.

Promoters of stone formation. A number of receptors or receptor-like features have been reported to play critical roles in crystal-cell interaction, which is recognized as the most important process for crystal retention in kidney (8,27). Recently, protein alterations in a CaOx monohydrate (COM) crystal-cell interaction model were screened by the authors, and 1,141 differentially expressed proteins (DEPs) were identified in COM treated HK-2 cells (28). Proteins and glycosaminoglycan like CD44, nucleolin, hyaluronan (HA), heat shock protein 90 (HSP90) (29), Annexin II (30) and osteopontin (OPN) (28,31), have been reported to act as stone

formation modulators, which has been thoroughly reviewed previously (32). Several structures and molecular components also play the role of receptor in crystal attachments, including the phosphatidylserine component of the lipid bilayer and the acidic side chains of proteins (33). Calcium, oxalate, urate and phosphate ions are the main promoters of crystal formation, which can promote crystallization of stone constituents or their aggregation through the activation of several mechanisms. Ketha *et al* (34) demonstrated that the first time nephrolithiasis patients had increased serum calcium and 1,25(OH)2D levels than the corresponding healthy individual serum calcium levels, suggesting that stone formation is a manifestation of altered calcium and vitamin D regulation. Higher serum calcium concentration acts as a promoter in lithogenesis, which directly regulated by the calcium-sensing receptor (CaSR) through different pathways (35). Similarly, urate and phosphate ions have also been reported to promote heterogeneous nucleation and enhance the attachment of crystals to epitheliums (36,37). Another important promoter of stone formation is urine pH (38). Low pH urine may lead to CaOx crystallization and crystal precipitation (39). High-alkaline urine may also promote precipitation and nucleation of CaOx crystals (40,41). Lysozyme and lactoferrin are two most recently identified proteins that promote COM growth through the acceleration of layer advancement rate on crystal surfaces (42).

Inhibitors of stone formation. Normal urine contains numerous inhibitors that act both in competition and cooperation, consequently decrease crystallization and inhibit crystals aggregation and/or adhesion to the tubular epithelial cells (43,44). These inhibitors can be divided into three groups: Anions, metallic cations and macromolecules. Anions such as citrate, can inhibit crystal growth very efficiently, at concentrations above 0.1 mM (45,46). A majority of nephrolithiasis patients exhibited a decrease in citrate excretion. Alkali supplements are widely used for hypocitraturic recurrent nephrolithiasis patients to restore citrate excretion (47,48). Hydroxycitrate is a structural analog of citrate, which has been reported to show equivalent capacity in forming complexes with calcium, in order to inhibit crystallization (49,50). Metallic cations such as magnesium, have been reported to inhibit crystal growth and aggregation, which is synergistic with citrate in acidic environments (51-53). Macromolecules are the most effective inhibitors of crystal growth. More specifically, OPN, Tamm-Horsfall protein (THP), urinary prothrombin fragment 1 (UPTF-1), nephrocalcin (NC) and some subunits of the serum IαI are able to inhibit crystal growth, aggregation and/or adhesion to the tubular cells (11,38,45).

However, there is a competition between supersaturation and inhibitors of crystallization as mentioned above, which ultimately determines the pattern of crystalluria in nephrolithiasis patients and healthy individuals (54). As a consequence of the increased promoters and reduced inhibitors, crystal formation and kidney stone occurrence have been observed (Fig. 1).

3. Randall's plaque and calcium oxalate stone formation

RPs, first proposed by Alexander Randall in 1937 (55), are regions of subepithelial mineralized tissue at the papillary tip,
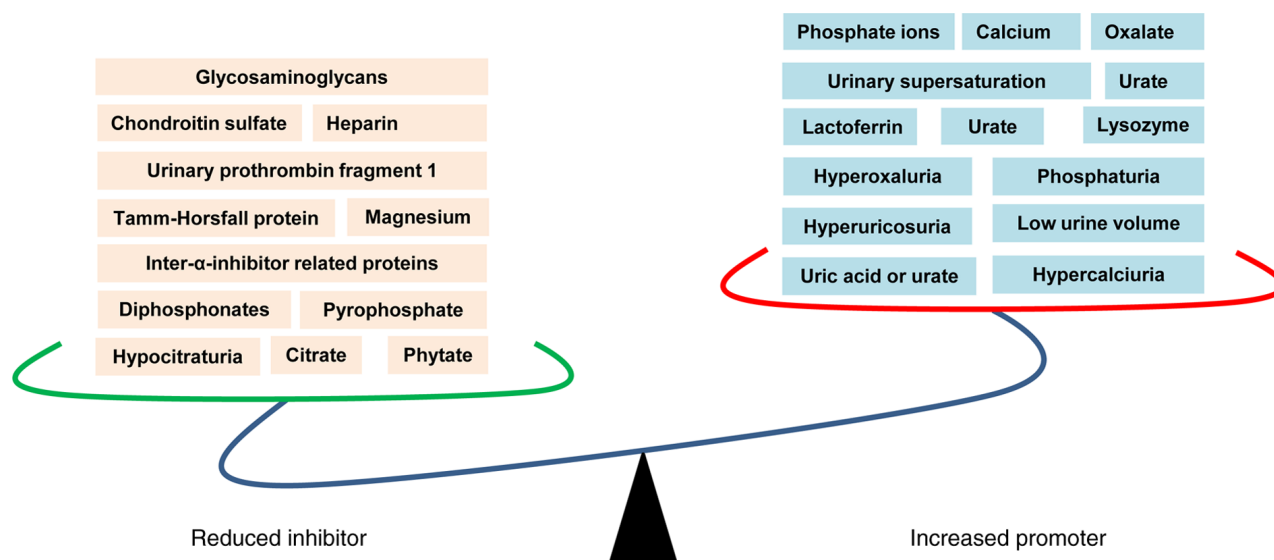
Figure 1. Physicochemical mechanisms of kidney stone formation. The reduced inhibitors (left panel) and increased promoters (right panel) are suggested to play critical roles in kidney stone formation.

surrounding the openings of the ducts of Bellini containing CaP (56). Scanning electron microscopy (SEM) examination has shown that RP are made of a mixing of tubules with calcified walls and of tubules obstructed by CaP plugs (57). RP consists of CaP crystals mixed with an organic matrix that is rich in various proteins and lipids, and includes membrane-bound vesicles or exosomes, collagen fibers, as well as other components of the extracellular matrix (58). An increasing number of studies have suggested that RPs are the origin of renal stones (57-60). Winfree *et al* (61) clarified that kidney stones develop as an overgrowth on RP, which contains unique organic composition (fibrillar collagen) that can be differentiated from the stone overgrowth by specific autofluorescence signatures. Of note, a previous study using a murine mode of RP revealed that vitamin D supplementation and calcium intake could notably accelerate RP formation (60). However, the precise mechanisms of RP formation remain unclear.

Recently, studies indicated that long non-coding RNAs (lcnRNAs) H19 and MALAT1 mediated osteogenic differentiation of human renal interstitial fibroblasts (hRIFs) and participated in RP formation (62-64). lcnRNA H19 has been shown to be significantly upregulated in RP, which can promote the osteogenic differentiation of hRIFs by activating Wnt/β-catenin signaling (63). lcnRNA H19 can also serve as a facilitator in the process of CaOx nephrocalcinosis-induced oxidative stress and renal tubular epithelial cell injury through the interaction with miR-216b and exerts its effect via the HMGB1/TLR4/NF-κB signaling pathway (64). lcnRNA MALAT1 can function as a competing endogenous RNA (ceRNA) that sponges miR-320a-5p, upregulates Runx2 expression and thus promotes the osteogenic phenotype of hRIFs (62).

These studies provide novel insight into the pathogenesis of RP-mediated kidney stone disease, while further studies are urgently anticipated to explore the mechanisms of RP formation, as well as additional roles of RP in the context of stone formation.

4. Role of sex hormones in calcium oxalate nephrolithiasis

Statistical analyses have revealed that males have a higher incidence of CaOx nephrolithiasis than females at a ratio of 2-3:1 (4,65); however, the exact mechanism remain unclear. Previous studies have indicated that androgens increase and estrogens decrease urinary oxalate excretion, plasma oxalate concentration and kidney CaOx crystal deposition. Additionally, enhanced androgen signaling may be responsible for the association between sex and kidney stone formation (65-68). Androgen receptor (AR) signaling can directly upregulate hepatic glycolate oxidase (69) and kidney epithelial nicotinamide adenine dinucleotide phosphate oxidase (NAPDH), subunit p22-PHOX at the transcriptional level, so as to increase oxalate biosynthesis, ultimately leading to kidney stone formation (70). Peng *et al* (71) reported that testosterone contributes to nephrolithiasis development through the induction of renal tubular epithelial cells apoptosis and necrosis through HIF-1α/BNIP3 pathway. Changtong *et al* (72) revealed that testosterone could promote kidney stone disease via the enhanced COM crystal-cell adhesion by the increased surface α-enolase. Zhu *et al* (73) demonstrated that AR can inhibit the recruitment of macrophages and suppress the COM crystals phagocytic ability of macrophages via the decrease of the colony-stimulating factor 1 (CSF-1) signals, through miR-185-5p upregulation. These findings suggest that androgen receptor signaling may be a key player in the development of nephrolithiasis (Fig. 2).

Theoretically, AR may be a new potential target and can be evaluated for novel therapeutics for the suppression of kidney stone formation. The 5α-reductase inhibitor, finasteride, has been reported to abolish the promoting effect of testosterone on COM crystallization (74). Another newly developed AR degradation enhancer, dimethylcurcumin (ASC-J9), has been reported to suppress oxalate crystal formation via the modulation of oxalate biosynthesis and reactive oxygen species (ROS)-induced kidney tubular epithelial cell injury in a rat model (73). Reversely, estrogen may serve as a
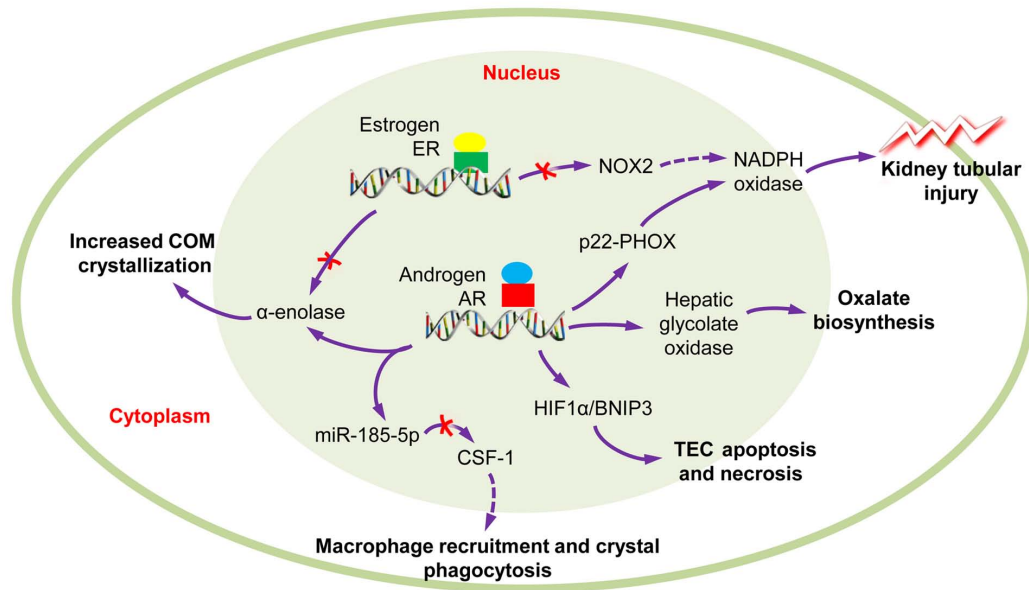
Figure 2. Role of sex hormones in calcium oxalate nephrolithiasis. The AR signaling could induce TECs apoptosis and necrosis and kidney tubular injury, promote COM crystallization and oxalate biosynthesis; however, macrophage recruitment and crystal phagocytosis are inhibited. Conversely, ER signaling can reduce ROS-mediated kidney tubular injury and COM crystallization. COM, calcium oxalate monohydrate; AR, androgen receptor; ER, estrogen receptor; ROS, reactive oxygen species.
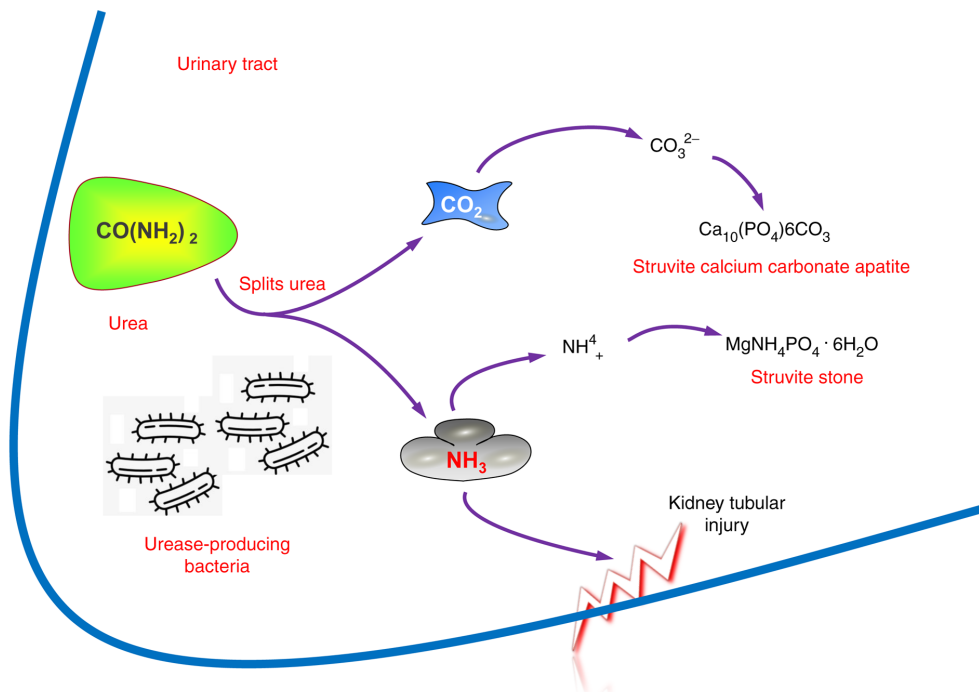

Figure 3. Role of urease-producing bacteria in stone formation. The urease-producing bacteria split urea and promote the formation of ammonia and carbon dioxide, leading to kidney tubular injury and urine alkalinization and subsequent formation of phosphate salts.

protective factor against kidney stone formation. An *in vitro* study demonstrated that estrogen led to changes in the cellular proteome of [Madin darby canine kidney (MDCK)] renal tubular cells that led to the decreased CaOx crystal receptor surface expression (annexin A1 and α-enolase), reduced intracellular ATP, and enhanced cell proliferation and renal tubular cell tissue healing (75). There is evidence to suggest that estrogen receptor β (ERβ) can suppress oxalate-induced oxidative stress via transcriptional suppression of the NADPH

oxidase subunit 2 (NOX2) through the direct binding to the estrogen response elements (EREs) on the NOX2 5' promoter (76), which exerts protective effects on renal CaOx crystal deposition.

All these findings may partly explain why a higher incidence of nephrolithiasis is encounter in males than in females. Targeting AR may be developed as a potential therapy for CaOx crystal-related kidney stone disease. However, these studies were performed *in vitro* and *in vivo*, using only cell
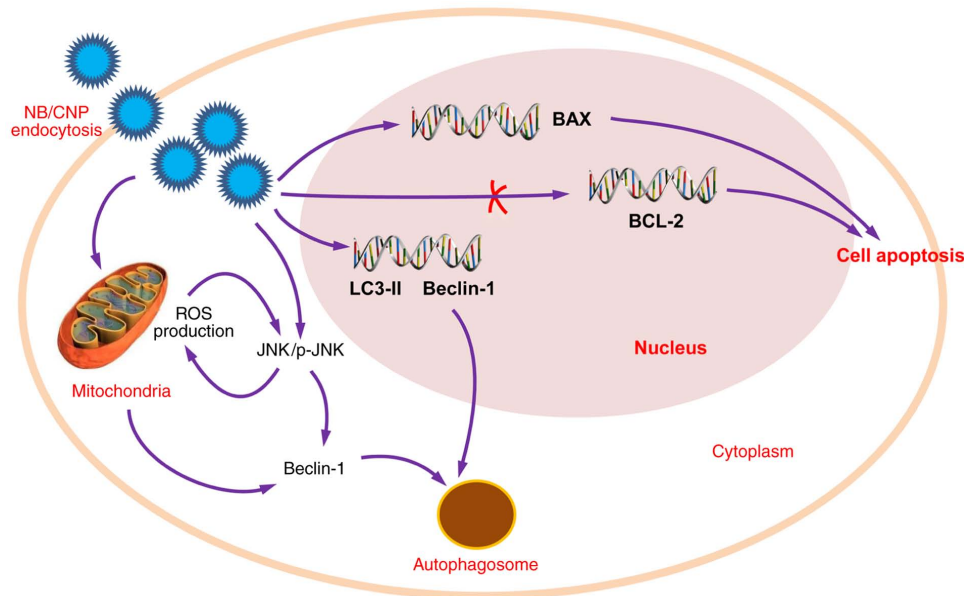
Figure 4. Role of nanobacteria in stone formation. The nanobacteria may induce ROS production through the JNK/p-JNK signaling induction, may decrease mitochondrial membrane potential and promote cell apoptosis through the downregulation of Bcl-2 expression and the upregulation of Bax expression. Additionally, nanobacteria may lead to autophagy through the upregulation of LC3-II and Beclin-1 expression. ROS, reactive oxygen species; LC3-II, microtubule-associated proteins 1A/1B light chain 3B.

lines or animal models. Further validation and clinical studies are required. Finasteride and ASC-J9 have been demonstrated to suppress a number of AR-mediated diseases, including prostate cancer (77,78), liver cancer and spinal and bulbar muscular atrophy neuron disease (79). However, additional future studies are necessary before the clinical application of finasteride and ASC-J9 in kidney stone prevention, considering the side-effects, including sexual dysfunction (80).

5. Role of the microbiome in stone formation

Emerging evidence has indicated that microorganisms belonging to the human microbiome, including microorganisms of the kidney and urinary tract, are likely to have a profound effect on urological health, both positive and negative, due to their metabolic output and other contributions (81).

Urease-producing bacteria. Urease-producing bacteria, such as *Proteus mirabilis, Klebsiella pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa, Providentia stuartii, Serratia* and *Morganella morganii*, are always associated with struvite stone formation and recurrence (82,83). The bacterial urease degrades urea and promotes ammonia and carbon dioxide formation, leading to urine alkalinization and phosphate salt formation (Fig. 3).

Urinary acidification and urease inhibitors have been proposed and implemented for the prevention and/or dissolution of struvite stones and encrustations in patients with infection by urea-degrading bacteria; however, their long term use is limited due to their ineffectiveness and toxicity (84). Secondarily infected stones caused by non-urease-producing bacteria, including *Escherichia coli* and *Enterococcus* spp., have also been described (85,86). However, whether kidney stones form and become secondarily infected or result from a nidus of infection that propagates stone formation remains largely unclear.
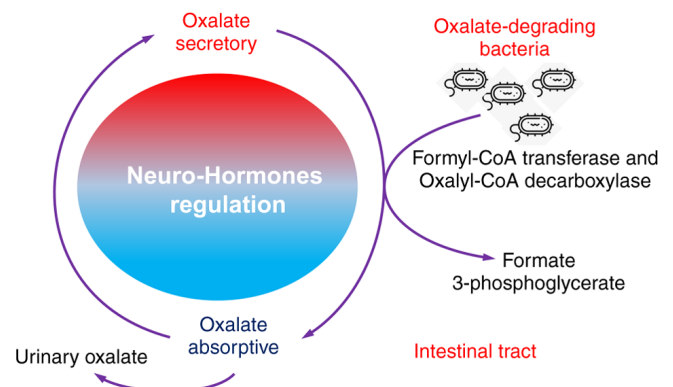

Figure 5. Role of oxalate-degrading bacteria in stone formation. Oxalate-degrading bacteria use oxalate as a carbon energy source and thrive in the presence of the oxalate anion, reduce urinary oxalate level and exhibit growth inhibition in the calcium oxalate crystallization in the kidney.

Nanobacteria (NB). NB have been isolated from kidney stones for >30 years (87-89); however, the nature and the mechanisms involved remain obscure. Ansari *et al* (90) demonstrated that the size of cultured NB varies between 60 and 160 nm, and that they could infect patients with apatite kidney stone. Kajander *et al* (91) indicated that NB can adapt to growing in plain DMEM or RPMI-1640, through self-proliferation. In the study by Ciftçioglu *et al* (92), it was demonstrated that 70 out of 72 (97.2%) kidney stones contained NB. The presence of NB was independent of the stone type, although apatite-based kidney stones presented the highest immunopositivity (91). NB are considered to play roles in calcium nucleation, as they can produce sufficient calcium apatite in their cell walls to initiate pathologic calcifications and stone formation (93-95). This evidence is strongly in favor of the suggestion that NB are living organisms.
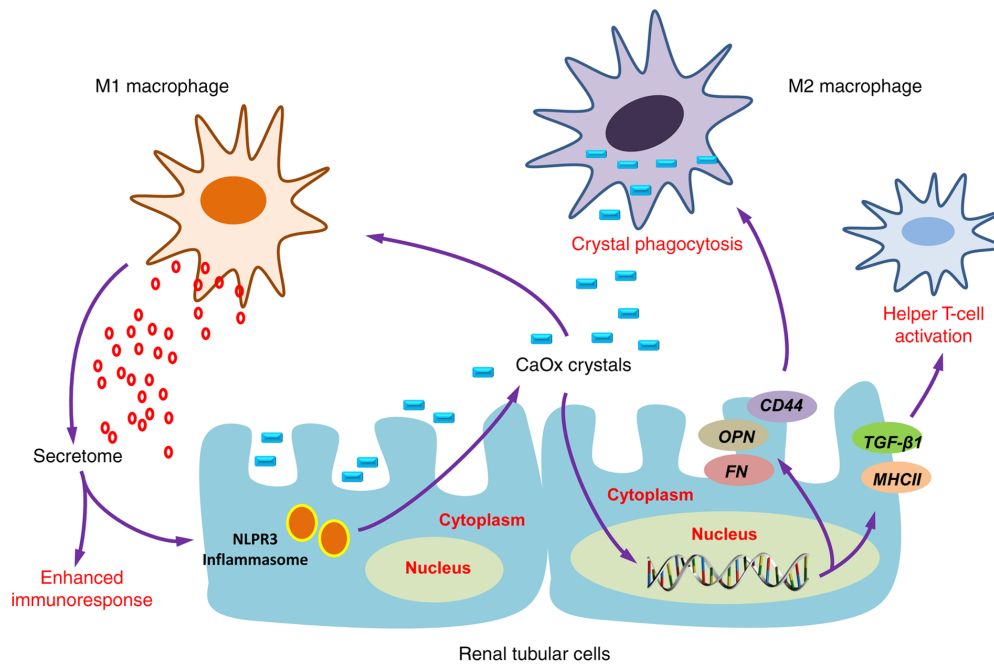
Figure 6. Immune response to urinary crystals. Macrophage accumulation and macrophage-related inflammation or anti-inflammation is the main immune response alteration observed as a result of kidney stone formation. M1 macrophages are important effectors of CaOx stone formation, while M2 macrophages could prevent CaOx inflammatory damage through crystal phagocytosis. CaOx, calcium oxalate.

However, an increasing number of studies have indicated that NB, also termed 'Calcifying nanoparticles (CNPs)', 'nanobacteria-like particles' or 'Nanobes', are merely mineral protein nanoparticles with biomimetic functions (88,89). Although the definition and nature of these nanoparticles remains controversial (96), their roles in kidney stone diseases has been widely reported. CNPs have been identified in RPs and have been proven to be cytotoxic to 3T6 fibroblasts and HK-2 cells *in vitro* (89), which contributes to the renal tubular epithelial cell injury linked to kidney stone formation. Hong *et al* (97) demonstrated that catalase (CAT) and malonaldehyde (MDA) levels were significantly higher in CNP-treated HK-2 cells than the HK-2 control group, suggesting that CNPs may induce lipid peroxidation and result in damaging HK-2 cells. Wu *et al* (89) demonstrated that the CNPs may: Induce ROS production through JNK activation; decrease mitochondrial membrane potential and promote cell apoptosis through the downregulation of Bcl-2 expression and the upregulation of Bax expression; lead to autophagy through the upregulation of microtubule-associated proteins 1A/1B light chain 3B (LC3-II) and Beclin-1 expression (Fig. 4).

According to currently available findings in the literature, NB are localized in high concentrations in kidneys, excreted in urine, are isolated from RPs and the majority of renal stones, and play the role of the initiator, by favoring nucleation and crystal formation. Continued investigations are required, in order to solve the controversy of whether NB are living or non-living, as well as the mechanisms through which NB induce calcification and stone formation.

Intestinal microbiota. The intestinal microbiome, which has been a recent area of wide interest, has been reported to play a role in both the pathogenesis and prevention of kidney stone disease (87,98-100). *Oxalobacter formigenes* is the most well-studied Gram-negative anaerobic bacterium that degrades oxalate in the intestinal tract and has potential probiotic characteristics for the prevention of CaOx kidney stone formation.

In a pilot study, Stern *et al* (101) investigated the distinct differences in the gut microbiome of nephrolithiasis patients, as compared with patients without kidney stone formation. Their results demonstrated that the genus *Bacteroides* were 3.4-fold more abundant in the kidney stone group, while the genus *Prevotella* were 2.8-fold more abundant in the non-stone control group. A 24 h urine analysis revealed that the genus *Eubacterium* was inversely associated with oxalate levels and the genus *Escherichia* trended to an inverse correlation with citrate level (101). However, the potential causative role of pre-existing dysbiosis of gut microbiome in kidney stone disease is still unclear, and the association of urinary oxalate excretion and oxalate-degrading bacteria abundances remain limited (87,98,102,103).

Both absorptive and secretory pathways for oxalate have been identified in the proximal and distal segments of the colon, regulated by neuro-hormones that direct net oxalate level. Thus, it has been suggested that intestinal tract participates significantly in oxalate balance and subsequent oxalate homeostasis (104-106). The intestinal tract is also where oxalate-degrading bacteria tend to reside, particularly *Oxalobacter formigenes*, which requires a strict anaerobic environment to survive. One hypothesis for the role of the microbiome in the prevention of kidney stone has been that specific functional bacteria, such as the oxalate-degrading bacteria (such as *Oxalobacter formigenes*, *Bifidobacterium* sp. *Porphyromonas gingivalis* and *Bacillus* sp.) in human gut and intestinal tract, which use oxalate as their carbon energy source and thrive in the presence of the oxalate anion, exhibit growth inhibition in the CaOx crystallization in the kidney (102,107,108) (Fig. 5).

The activity of oxalate-degrading bacteria mediates extra-renal elimination of oxalate in the intestines and has a significantly impact on the homeostatic levels of oxalate in plasma and urine (109). This activity exhibits a strong association with the occurrence of CaOx stone formation.

6. Immune response to urinary crystals

Macrophage accumulation and macrophage-related inflammation or anti-inflammation is the main immune response alteration observed in kidney stone disease, which has been widely reported to play a crucial role in renal CaOx crystal formation (110).

Firstly, the recruited macrophages could promote the development of COM crystals via the interaction of CD44 with OPN and fibronectin (FN) (111), which are upregulated in renal tubular cells induced by crystals. Secondly, macrophages have been evidenced to secrete various mediators via classical secretory pathways that cause renal interstitial inflammation (112,113), particularly macrophage inhibitory protein-1, monocyte chemoattractant protein-1 and interleukin-8 (IL-8) (112). These chemokines consequently enhance the recruitment of various immune cells, including monocytes, macrophages, neutrophils, dendritic cells and T-cells into the inflammatory locale (114,115). Several studies have demonstrated that macrophage-derived exosomes following COM exposure are involved in kidney stone pathogenesis (112,113,116). A set of proteins in COM-treated macrophage exosomes were previously identified as proteins involved mainly in immune processes, including T-cell activation and homeostasis, Fcγ receptor-mediated phagocytosis, interferon-γ (IFN-γ) regulation and cell migration (112). Additionally, infiltrated monocytes could differentiate into different macrophage subtypes with a wide range of clinical manifestations, presentations and histological phenotypes (110,117), display protective or pathogenic activities in kidney stone development (110).

Increasing evidence has revealed that M1/M2-macrophage differentiation plays an important role in renal CaOx crystal formation (111,115,118-120). However, whether M1 macrophage-mediated inflammation that contributes to stone formation will initiate stone promoters and reduce stone inhibitors remains controversial. Khan et al (58) demonstrated that M1 macrophages could cause acute tissue injury, which was associated with crystal deposition and RP formation. Conversely, Taguchi et al (121) concluded that there was no association between renal dysfunction and increased crystal deposition, based on their observation that no changes were observed in urinary variables in lipopolysaccharide (LPS)-induced M1 macrophage-mediated acute renal injury. M2 anti-inflammatory macrophages can phagocytize and degrade CaOx kidney stone fragments through a clathrin-dependent mechanism (110,113,115,120,121) (Fig. 6).

Given the critical role of immune-response in CaOx crystal formation and development, the immunotherapy approach has been proposed to prevent stone recurrences in certain individuals through the modulation of the immune response, in order to degrade CaOx crystals and thus prevent stones from developing (122). However, investigations into immunotherapeutic targets for kidney stone disease are urgently required.

7. Conclusion and future perspectives

In the present review article, emerging concepts of mechanisms contributing to stone formation were summarized, by reviewing novel insight into kidney stone disease related-metabolic risk factors, receptors, promoters and inhibitors, through the examination of the roles of immune-response, microbiome and sex hormones in stone formation and development. The pathophysiology of kidney stone disease cannot be completely explained by crystallization processes alone. However, due to current limitations in research, there are still some research areas in kidney stone formation that remain poorly understood, and were not been discussed herein. Future comprehensive studies are mandatory to further elucidate the mechanisms of the microbiome and immune response in kidney stone formation, in order to develop novel prophylactic and therapeutic approaches.

Availability of data and materials

Not applicable.

Authors' contributions

ZW and YZ prepared and drafted the manuscript. ZW obtained funding for the study, and drafted and revised the manuscript. QD, JZ and HL assisted in obtaining data for the review article, drafted the manuscript and provided critical revision of the manuscript for intellectual content. ZW and HL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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