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Role of oxidative stress and reactive oxygen species in calcium oxalate kidney stone pathogenesis

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ABSTRACT

Oxidative stress and reactive oxygen species (ROS) generation are central drivers of calcium oxalate kidney stone pathogenesis by promoting renal tubular epithelial cell injury, inflammation, cell death, and extracellular matrix remodeling, which collectively create a renal environment conducive to crystal deposition, retention, and stone growth. Targeting oxidative stress pathways with antioxidants and modulators of ROS production presents a promising avenue for therapeutic intervention to prevent kidney stone recurrence and progression. This insights from molecular, cellular, and pathophysiological studies showing that calcium oxalate crystals set off a cascade of oxidative and inflammatory events that culminate in kidney stone formation, and also accentuates the importance of maintaining redox balance and renal cellular health in mitigating the burden of calcium oxalate nephrolithiasis.

Keywords: Oxidative stress, Kidney stone, Reactive oxygen species, Nephrolithiasis, Calcium oxalate stone, Endothelial dysfunction, Antioxidant

Implication for health policy/practice/research/medical education:
Oxidative stress and reactive oxygen species (ROS) play an intricate role in the pathogenesis of calcium oxalate kidney stones, from initial cellular injury and inflammation to crystal adhesion and growth. The complex interplay of reactive oxygen species generation, antioxidant defenses, mitochondrial dysfunction, and endoplasmic reticulum stress collectively drives this pathological process.

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Introduction

Calcium oxalate kidney stones represent the most prevalent form of nephrolithiasis in humans, accounting for approximately 70%–80% of all urinary stones (1,2). Despite decades of research into their formation, the precise molecular and cellular mechanisms driving crystal nucleation, growth, aggregation, and retention within the renal tubules remain incompletely understood (3). Historically, stone formation was viewed as a purely physicochemical phenomenon governed by urinary super-saturation of calcium and oxalate ions (4). However, accumulating evidence over the past two decades has increasingly implicated biological factors particularly oxidative stress and reactive oxygen species (ROS), as critical mediators in the pathogenesis of calcium oxalate nephrolithiasis (5). This evolving paradigm positions oxidative stress not merely as a bystander but as a central orchestrator of renal epithelial injury, inflammation, crystal adhesion, and fibrosis, all of which facilitate stone development and recurrence (6). This overview sought to test role of oxidative stress and ROS in calcium oxalate kidney stone pathogenesis.

Search strategy

For this narrative review, we conducted a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase, using a variety of relevant keywords like 'oxidative stress', 'kidney stone', 'reactive oxygen species', 'endothelial dysfunction', 'nephrolithiasis', 'antioxidant' and 'calcium oxalate stones'.

Oxidative stress in the kidney

Oxidative stress arises when the production of ROS overwhelms the antioxidant defense systems of cells, leading to damage of lipids, proteins, and DNA (7). ROS

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are chemically reactive molecules containing oxygen, including superoxide anion ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and peroxynitrite ($ONOO^-$) (8). Since, low levels of ROS serve as signaling molecules in physiological processes such as cell proliferation, immune response, and apoptosis (9); however, excessive or sustained ROS production triggers pathological cascades (10). In the context of calcium oxalate stone formation, hyperoxaluria, whether dietary, enteric, or genetic serves as a primary instigator of ROS generation (11). Elevated oxalate concentrations, even in the absence of crystal formation, have been shown to induce oxidative stress in renal tubular epithelial cells both in vitro and in vivo (12). Then oxalate-induced oxidative stress initiates a cascade of cellular events that promote crystal retention and stone growth (5).

Previous studies found that, the proximal tubule and the collecting duct are particularly vulnerable to oxalate toxicity due to their roles in oxalate transport and concentration (13). Exposure of renal epithelial cells to oxalate leads to mitochondrial dysfunction, resulting in electron leakage from the electron transport chain and consequent superoxide generation (14). Mitochondria are both sources and targets of ROS, and their impairment under hyperoxaluric conditions amplifies oxidative damage (15). Additionally, oxalate activates membrane-bound NADPH oxidases (NOX enzymes), particularly NOX4, which is constitutively expressed in the kidney and further upregulated in response to oxalate exposure (16). NOX4-derived superoxide and hydrogen peroxide contribute significantly to intracellular oxidative stress and activate downstream pro-inflammatory and pro-fibrotic pathways (17).

The consequences of oxidative stress in renal epithelial cells exposed to oxalate or calcium oxalate crystals are manifold (11). When lipid peroxidation occurs, disrupting membrane integrity and fluidity (11). This event compromises the barrier function of tubular cells and facilitates the adherence of calcium oxalate crystals to the apical surface (18). At this condition, malondialdehyde and 4-hydroxynonenal, products of lipid peroxidation, will be consistently strengthened in the urine and renal tissues of stone formers and experimental models of hyperoxaluria (19,20). These aldehydes are not merely markers of oxidative damage but also act as signaling molecules that modulate gene expression, induce apoptosis, and promote inflammation (19,20). In addition, oxidative stress induces DNA damage, triggering activation of poly (ADP-ribose) polymerase (PARP), a nuclear enzyme involved in DNA repair (21). Then, over-activation of PARP depletes cellular NAD^+ and ATP, leading to energy failure and necrotic cell death (22). This form of cell death releases intracellular contents, including nucleic acids, proteins, and membrane fragments, which serve as nucleation sites for calcium oxalate crystals (23). Moreover, dying cells expose phosphatidylserine on their outer membrane leaflet, a known ligand for crystal binding (24). Thus, oxidative stress-induced cell death directly promotes crystal retention by providing anchoring sites and organic matrices for heterogeneous nucleation (25). Likewise, oxidative stress triggers the activation of redox-sensitive transcription factors such as nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), and hypoxia-inducible factor-1α (26). These transcription factors regulate the expression of numerous pro-inflammatory cytokines, chemokines, and adhesion molecules (26). For instance, NF-κB activation leads to increased expression of monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) (27). These mediators recruit macrophages, neutrophils, and other immune cells to the site of crystal deposition, amplifying local inflammation (28). In fact, inflammation is initially a protective response aimed at clearing crystals and repairing tissue (29); however, chronic or dysregulated inflammation contributes to tubular atrophy, interstitial fibrosis, and progressive renal damage, conditions that paradoxically favor recurrent stone formation by altering urinary flow dynamics and promoting crystal retention (30).

Beyond promoting inflammation, oxidative stress modulates the expression of crystal-binding molecules on the surface of renal epithelial cells (11). One such molecule is osteopontin, a phosphorylated glycoprotein that is upregulated in response to oxidative stress and crystal exposure (31). Osteopontin exhibits dual roles: it can inhibit crystal growth and aggregation at low concentrations but promotes crystal adhesion and retention when over-expressed or immobilized on injured cell surfaces (32). Oxidative modification of properties of osteopontin, such as carbonylation or nitration, may alter its conformation and functional properties, enhancing its affinity for calcium oxalate crystals. Other crystal-binding molecules influenced by oxidative stress include hyaluronan, CD44, and annexin II, all of which are upregulated under conditions of ROS overproduction and contribute to crystal-cell interactions (33,34).

Role of oxidative stress in calcium oxalate stones

The role of oxidative stress in calcium oxalate stone pathogenesis is further supported by studies demonstrating that antioxidants can attenuate crystal formation and renal injury in experimental models (11). Administration of antioxidants such as vitamin E, N-acetylcysteine (NAC), melatonin, resveratrol, quercetin, and superoxide dismutase mimetics has been shown to reduce urinary markers of oxidative stress, decrease crystal deposition, suppress inflammatory cytokine expression, and preserve renal function in hyperoxaluric rats and mice (35). These findings suggest that oxidative stress is not merely correlative but causally involved in stone formation (36). Importantly, some antioxidants also inhibit NADPH

oxidase activity or enhance endogenous antioxidant defenses such as glutathione (GSH), catalase, and heme oxygenase-1 (HO-1), thereby interrupting the vicious cycle of ROS generation and tissue injury (37).

Clinical evidence also supports the involvement of oxidative stress in human calcium oxalate stone formers (38). Compared to healthy individuals, stone formers exhibit elevated levels of urinary and serum markers of oxidative damage, including 8-hydroxy-2'-deoxyguanosine (8-OHdG, a marker of DNA oxidation), F2-isoprostanes (markers of lipid peroxidation), and protein carbonyls (30, 39). Conversely, levels of antioxidant enzymes and molecules, such as SOD (superoxide dismutase), catalase, GSH, and uric acid are often reduced in recurrent stone formers (40). These biochemical alterations correlate with stone burden, recurrence rate, and degree of renal injury, suggesting that the magnitude of oxidative stress may serve as a prognostic indicator in nephrolithiasis (41).

Furthermore, genetic polymorphisms in antioxidant defense genes have been associated with increased susceptibility to calcium oxalate stones (11). Variants in genes encoding superoxide dismutase, GPx (glutathione peroxidase), catalase, and NAD(P)H:quinone oxidoreductase 1 (NQO1) have been linked to higher stone risk in certain populations (4, 42). These polymorphisms may result in reduced enzymatic activity or expression, rendering individuals more vulnerable to oxalate-induced oxidative damage (5). Similarly, mutations in genes involved in oxalate metabolism like AGXT (alanine-glyoxylate aminotransferase) in primary hyperoxaluria lead to massive oxalate overproduction and consequent oxidative stress, culminating in early-onset and aggressive stone disease (43).

Recent studies demonstrated that, oxidative stress also intersects with other pathogenic pathways in calcium oxalate nephrolithiasis (3). Oxidative stress activates the renin-angiotensin-aldosterone system (RAAS), which is known to promote renal fibrosis and inflammation (44). Angiotensin II, as the primary effector of RAAS, stimulates NADPH oxidase activity, further amplifying ROS production (44). This condition creates a feed-forward loop in which oxidative stress and RAAS activation mutually reinforce each other, accelerating renal injury and stone formation (30). Inhibitors of angiotensin-converting enzyme (ACE) or angiotensin II type 1-receptor blockers have been shown to reduce crystal deposition and oxidative damage in animal models, highlighting the therapeutic potential of targeting this axis (45).

Another critical intersection is with autophagy, a cellular recycling process that removes damaged organelles and proteins (46). Oxidative stress impairs autophagic flux in renal tubular cells, leading to accumulation of dysfunctional mitochondria (mitophagy failure) and protein aggregates (47). This disorder not only exacerbates ROS production but also promotes inflammasome activation, particularly the NLRP3 inflammasome, which processes pro-IL-1β into its active form, driving sterile inflammation in response to crystals (47). Inhibition of autophagy or inflammasome components reduces crystal-induced inflammation and injury in experimental models, underscoring the importance of this pathway in stone pathogenesis (46).

Several investigations detected that, endoplasmic reticulum stress represents another consequence of oxidative stress in calcium oxalate stone formation (48). Accumulation of misfolded proteins due to oxidative damage triggers the unfolded protein response, which, if unresolved, leads to apoptosis by CHOP (C/EBP homologous protein) activation (49). Endoplasmic reticulum stress markers such as GRP78, ATF4, and XBP1 are elevated in renal tissues exposed to oxalate or calcium oxalate crystals (48). Pharmacological inhibition of endoplasmic reticulum stress attenuates cell death and crystal adhesion, suggesting that targeting endoplasmic reticulum stress may be a viable therapeutic strategy (50).

Oxidative stress and epigenetic modifications

The interplay between oxidative stress and epigenetic modifications further complicates the pathogenesis of calcium oxalate stones (51). Oxidative DNA damage and altered redox states can influence DNA methylation patterns, histone modifications, and microRNA expression (52). In this regard, oxidative stress has been detected to down-regulate the expression of miR-155 and miR-146a, which normally suppress inflammatory signaling (53). Conversely, it upregulates miR-21, which promotes fibrosis by targeting PTEN and enhancing Akt signaling (54). These epigenetic changes may contribute to the persistence of pro-inflammatory and pro-fibrotic phenotypes in renal epithelial cells, even after the initial insult has subsided, thereby facilitating recurrent stone formation (28).

Focus on epithelial-to-mesenchymal transition

In the context of crystal retention, oxidative stress promotes epithelial-to-mesenchymal transition (EMT) in renal tubular cells (55). Previous investigations found that, EMT is a process by which epithelial cells lose their polarity and cell-cell adhesion and acquire migratory and invasive mesenchymal properties (56). Though EMT is essential in embryonic development and wound healing, its aberrant activation in chronic kidney disease contributes to fibrosis and architectural distortion (57). Oxidative stress induces EMT through TGF-β1/Smad, Wnt/β-catenin, and Notch signaling pathways (58). Then, cells undergoing EMT exhibit altered expression of adhesion molecules and extracellular matrix components, creating a microenvironment conducive to crystal anchoring and growth (59,60). Additionally, mesenchymal-like cells secrete higher levels of properties of osteopontin, collagen I, and fibronectin, all of which serve as crystal-

binding substrates (61). Indeed, the role of oxidative stress extends beyond tubular epithelial cells to include renal interstitial cells, endothelial cells, and infiltrating immune cells (62). Macrophages exposed to calcium oxalate crystals undergo polarization toward a pro-inflammatory M1 phenotype, characterized by increased ROS production, cytokine secretion, and impaired phagocytic capacity (63). This situation not only perpetuates local inflammation but also contributes to oxidative damage of surrounding parenchyma (28). Endothelial dysfunction, another consequence of oxidative stress, impairs renal microcirculation and promotes hypoxia, which in turn induces hypoxia-inducible factor-1α and further ROS generation (64). Hypoxia also upregulates the expression of Randall's plaque components, such as interstitial calcium phosphate deposits, which serve as nucleation sites for calcium oxalate stones in the papilla (65).

Impact of oxidative stress in Randall's plaques

Randall's plaques are sub-epithelial calcifications that originate in the thin loops of Henle and extend to the papillary surface (66). Recent studies detected that oxidative stress may play a role in their formation (66). Chronic oxidative damage to the basement membrane and interstitial matrix may facilitate calcium phosphate deposition by exposing nucleation-promoting sites and altering local pH and ion concentrations (67). Moreover, oxidative stress-induced apoptosis of papillary epithelial cells may expose underlying plaque to the urinary space, allowing calcium oxalate crystals to anchor and grow into clinically significant stones (11). This mechanism may explain why stones attached to Randall's plaques are more common in idiopathic calcium oxalate stone formers, who often exhibit subtle but persistent oxidative stress despite normal urinary oxalate levels (5,68).

Gut dysbiosis, oxidative stress and nephrolithiasis

The microbiome also interacts with oxidative stress in the context of nephrolithiasis (69). Gut dysbiosis, which commonly observed in stone formers alters oxalate metabolism by reducing the abundance of oxalate-degrading bacteria such as *Oxalobacter formigenes* (70). This setting leads to increased intestinal oxalate absorption and subsequent hyperoxaluria (70,71). Dysbiosis also promotes intestinal barrier dysfunction and systemic inflammation, which can exacerbate renal oxidative stress (72). Conversely, probiotics and prebiotics that restore microbial balance have been shown to reduce urinary oxalate excretion and oxidative stress markers in both animals and humans, suggesting a gut-kidney axis in stone pathogenesis (69).

Therapeutic modalities pointing oxidative stress

Therapeutic strategies targeting oxidative stress in calcium oxalate nephrolithiasis are gaining traction (73). Beyond traditional antioxidants, novel approaches include mitochondrial-targeted antioxidants (e.g., MitoQ), NOX inhibitors (like apocynin, GKT137831), Nrf2 activators (like, sulforaphane, bardoxolone methyl), and SOD/catalase mimetics (74). Recent studies found that, Nrf2 (nuclear factor erythroid 2-related factor 2) is a master regulator of antioxidant response elements (ARE) and controls the expression of several cytoprotective genes (75). Activation of Nrf2 by pharmacological inducers enhances cellular resilience to oxidative stress and has shown promise in reducing crystal deposition and renal injury in preclinical models (76). Clinical trials evaluating Nrf2 activators in chronic kidney disease may provide insights into their utility in nephrolithiasis (77). Lifestyle modifications also play a crucial role in mitigating oxidative stress (78). Accordingly, adequate hydration dilutes urinary oxalate and reduces crystal super-saturation while simultaneously lowering the concentration of pro-oxidants (79). Dietary interventions rich in fruits, vegetables, and polyphenols (e.g., berries, green tea and curcumin) enhance antioxidant capacity and suppress inflammation (80). Conversely, high intake of animal protein, sodium, and fructose, which are common in Western diets promotes hypercalciuria, hyperoxaluria, and oxidative stress, thereby increasing stone risk (81). Meanwhile, weight loss in obese individuals reduces systemic inflammation and oxidative stress, which may explain the lower stone incidence observed after bariatric surgery despite the risk of enteric hyperoxaluria (82).

Recent evidence also implicates circadian rhythms in the regulation of oxidative stress and stone formation (83). Disruption of circadian clocks as seen in shift workers or individuals with sleep disorders alters the expression of antioxidant enzymes and oxalate transporters, leading to diurnal fluctuations in urinary super-saturation and oxidative stress (83). Moreover, chronotherapeutic approaches that align antioxidant administration with peak oxidative stress periods may enhance efficacy and reduce stone recurrence (84).

Conclusion

This review showed that, both oxidative stress and ROS are not peripheral players but also have a central role in the pathogenesis of calcium oxalate kidney stones. They initiate and perpetuate a cascade of events, from epithelial injury and crystal adhesion to inflammation, fibrosis, and epigenetic reprogramming, which create a permissive environment for stone nucleation and growth. The recognition of oxidative stress as a unifying mechanism underlying diverse etiologies of calcium oxalate nephrolithiasis, including idiopathic, dietary, genetic, and metabolic forms opens new avenues for prevention and treatment. Future research should focus on identifying reliable biomarkers of renal oxidative stress, developing targeted antioxidant therapies with minimal side effects, and integrating redox biology into personalized stone management strategies. Furthermore, it becomes

increasingly clear that combating oxidative stress may hold the key to breaking the cycle of stone recurrence and preserving long-term renal health.

Authors' contribution

Conceptualization: Paniz Pourpashang and Hamid Nasri.
Data curation: Paniz Pourpashang and Hamid Nasri.
Funding acquisition: Paniz Pourpashang and Hamid Nasri.
Investigation: Paniz Pourpashang and Hamid Nasri.
Methodology: Paniz Pourpashang and Hamid Nasri.
Project administration: Paniz Pourpashang and Hamid Nasri.
Supervision: Paniz Pourpashang and Hamid Nasri.
Validation: Paniz Pourpashang and Hamid Nasri.
Writing—original draft: PPaniz Pourpashang and Hamid Nasri.
Writing—review and editing: Paniz Pourpashang and Hamid Nasri.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Conflicts of interest

The authors declare that they have no competing interests.

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