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REVIEW
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SGLT2 inhibitors in nephrolithiasis: a paradigm shift in prevention and management

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ABSTRACT

Kidney stone disease (nephrolithiasis) is a prevalent, recurrent condition often underpinned by modifiable metabolic risk factors such as hypocitraturia, hyperuricosuria, and low urinary pH. Although prevention through dietary and pharmacologic interventions is possible, it remains inconsistently applied in clinical practice. Sodium–glucose co-transporter 2 inhibitors (SGLT2i), originally developed for glycemic control in type 2 diabetes, have shown unexpected effects on renal metabolism and acid-base handling, prompting interest in their potential utility in stone prevention. SGLT2i promotes glycosuria and shift in acid–base balance, which may increase urinary citrate and pH—both protective against stone formation. They also reduce serum uric acid and may exert favorable effects on urinary volume and calcium handling. These mechanisms suggest a growing therapeutic role in selected patients with nephrolithiasis, especially those with comorbid diabetes, chronic kidney disease (CKD), or hypocitraturia. While direct clinical data on stone recurrence under SGLT2i therapy are still limited, mechanistic consistency across preclinical and clinical studies is compelling. SGLT2 inhibitors are thus emerging as a promising pharmacologic strategy for nephrolithiasis prevention, particularly in patients with overlapping metabolic or renal indications. Ongoing mechanistic studies and prospective trials are expected to confirm their role as part of a personalized approach to stone disease management.

Keywords: Calcium oxalate, Calcium phosphate, Inflammation, Nephrolithiasis, Randall's plaque, SGLT2 inhibitors, Urinary citrate, Urinary pH, Uric acid

Introduction

Kidney stone disease, or nephrolithiasis, is a prevalent and recurrent condition affecting nearly 10% of adults worldwide. While calcium oxalate (CaOx) stones are the most common type, other compositions such as calcium phosphate (CaP) and uric acid (UA) contribute significantly to disease heterogeneity and therapeutic complexity (1,2).

Recent insights have redefined nephrolithiasis as a systemic disorder involving metabolic, inflammatory, and epithelial factors, rather than merely a physicochemical imbalance in urine (2,3). Molecular and genetic studies have illuminated the interplay between renal tubular transport, immune cell activation, oxidative stress, and epithelial injury in stone formation (2-8).

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a class of antidiabetic drugs that reduce glucose and sodium reabsorption in the proximal tubule, promoting glucosuria and natriuresis (9). These agents have shown robust cardiorenal protective effects and a favorable safety profile in diverse populations (9,10). Their impact on urinary composition—including increased citrate, pH modulation, and reduced uric acid—has raised interest in their potential for kidney stone prevention.

Furthermore, preclinical data suggest that SGLT2i may exert anti-inflammatory and tubuloprotective effects, modulating key pathways involved in Randall's plaque formation and crystal retention (2,7-10). These actions offer a novel pathophysiological rationale for their use in nephrolithiasis, particularly among patients with diabetes, metabolic syndrome, or hypocitraturia.

To date, no other comprehensive review has synthesized the available mechanistic, preclinical, and clinical evidence linking SGLT2 inhibitors to stone prevention. This article aims to fill that gap by providing an updated, multidisciplinary overview of the rationale, emerging data, and potential clinical applications of SGLT2i in nephrolithiasis management.

Search strategy

This narrative review was conducted by searching PubMed, Scopus, and Web of Science for English-language articles published between January 2010 and June 2025. Search terms included "SGLT2 inhibitors", "sodium-glucose co-transporter 2",

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"kidney stones", "nephrolithiasis", "hypocitraturia", and "urinary citrate". We included original studies (preclinical, translational, and clinical) focusing on the pathophysiological, metabolic, or anti-inflammatory effects of SGLT2 inhibitors relevant to nephrolithiasis prevention. Additional references were identified through manual screening of bibliographies and relevant reviews. Due to the narrative nature of this review, no formal quality assessment or meta-analysis was performed.

Calcium oxalate stone pathogenesis: inflammation and immunity in randall's plaque

Recent advances in molecular and imaging techniques have shown that Randall's plaques are not inert mineral residues but dynamic and biologically active structures. Inflammatory and immune mechanisms play a pivotal role in the formation of calcium oxalate stones, the most common type of kidney stones (2).

Histological and molecular studies have demonstrated the presence of intact nuclei within Randall's plaques, staining positive for vimentin and CD45, markers of mesenchymal and hematopoietic origin. These findings suggest that both epithelial and immune cells contribute to plaque development (11). Collagen fibers have been identified within interstitial apatite deposits, but not in the overlying calcium oxalate layers, highlighting the importance of the extracellular matrix in initiating crystal nucleation (11).

Khan and colleagues proposed that plaques originate from calcification of basement membranes in the loops of Henle and the vasa recta, a process resembling vascular ossification. This involves interstitial calcium phosphate deposition driven by oxidative stress, apoptosis of tubular cells, and osteogenic transformation of interstitial cells (12).

When the overlying urothelium is damaged, these plaques become exposed to urine, transforming into anchoring sites for calcium oxalate crystal adherence and growth. This exposure promotes immune cell recruitment, particularly of classically activated (M1) macrophages, which release reactive oxygen species and inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-1 beta, thereby amplifying local tissue injury and promoting crystal retention (13,14). These macrophages also release exosomes enriched in vimentin and other inflammatory mediators, contributing to epithelial damage and crystal aggregation (13).

Khan's group also emphasized that epithelial cell damage or apoptosis may expose collagenous and mineralized surfaces, fostering heterogeneous nucleation and anchoring of calcium oxalate crystals (12).

Histological and molecular studies of the renal papilla in stone formers have demonstrated activation of inflammatory, oxidative stress, and extracellular matrix remodeling pathways (2,15). These immune-active regions—so-called "immune hotspots"—create a permissive microenvironment for plaque maturation and subsequent stone formation.

While M1 macrophages dominate in the acute inflammatory phase, other immune cells, such as mast cells and alternatively activated (M2) macrophages, may be involved in tissue remodeling and repair. However, their specific roles remain poorly defined (16).

Proteins such as matrix Gla protein, osteopontin, and fetuin-A are thought to stabilize calcium phosphate crystals and regulate interactions with the extracellular matrix. Their urinary excretion could serve as early markers of stone-forming activity, further supporting the concept of nephrolithiasis as an active immuno-inflammatory process rather than a purely physicochemical disorder (Figs 1A and B).

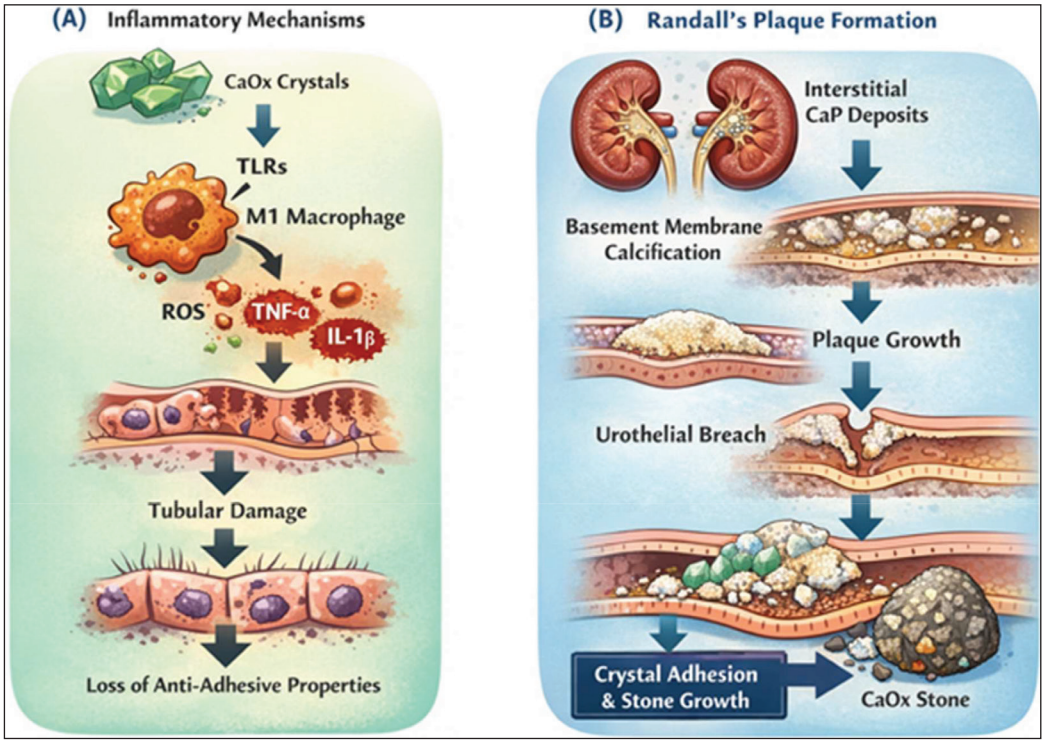

FIGURE 1 - (A) Inflammatory and immune mechanisms in Randall's plaque pathogenesis. CaOx crystals activate M1 macrophages via toll-like receptors, triggering the release of pro-inflammatory mediators (ROS, TNF-α, IL-1β) that promote tubular epithelial injury and loss of anti-adherent properties of the urothelium. (B) Sequential events leading to Randall's plaque formation and CaOx stone development: from interstitial apatite deposition to epithelial breach, immune cell recruitment, and inflammatory amplification, culminating in crystal adhesion, retention, and progressive stone growth at the papillary surface.

Although it remains unclear whether sodium-glucose co-transporter 2 inhibitors directly modulate these inflammatory pathways, their known anti-inflammatory and tubuloprotective effects provide a rationale for exploring their impact on Randall's plaque formation and progression.

These findings support the evolving concept of Randall's plaques as dynamic, immunologically active niduses of stone formation, driven by cellular stress, inflammation, and tissue remodeling (12).

Pathophysiological mechanisms and rationale for the use of SGLT2 inhibitors in nephrolithiasis

Kidney stone formation is a multifactorial condition, resulting from an intricate interplay of urinary supersaturation, metabolic abnormalities, and immune-mediated epithelial injury. Recent evidence suggests that sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors), beyond their glycemic action, may exert broader biological effects that reduce multiple lithogenic risk factors. These properties provide a compelling rationale for their potential use in the prevention of kidney stone disease (17).

However, it should be acknowledged that much of the direct mechanistic and interventional evidence currently available—particularly from the SWEETSTONE trial—derives from empagliflozin. Although several of these actions are likely related to shared pharmacodynamic properties of the SGLT2 inhibitor class, the extent to which they are fully generalizable across different agents remains to be established.

Reduction of urinary calcium excretion

SGLT2 inhibitors are associated with decreased urinary calcium excretion through indirect modulation of tubular calcium transport. Khan and colleagues highlighted the relevance of calcium transport proteins—such as TRPV5/6, claudin-14, and the calcium-sensing receptor (CaSR)—in idiopathic hypercalciuria. While not directly influenced by SGLT2 inhibitors, these transporters may be modulated via natriuretic and hemodynamic effects (12).

By reducing proximal sodium reabsorption, SGLT2 inhibitors induce mild natriuresis and alter downstream tubular sodium handling, which may secondarily influence calcium transport along the nephron (18). Rather than directly reducing calcium delivery, these changes are thought to modulate the balance between proximal and distal calcium reabsorption. Enhanced distal sodium reabsorption, driven by aldosterone, increases transcellular calcium reabsorption via TRPV5 channels. Additionally, by improving insulin sensitivity and mitigating hyperfiltration, SGLT2 inhibitors may further reduce filtered calcium load in patients with diabetes.

Increased urinary citrate excretion

Citrate inhibits calcium salt crystallization by chelating calcium ions and increasing urinary pH. SGLT2 inhibitors may increase urinary citrate by altering proximal tubule sodium–citrate co-transport. In the SWEETSTONE trial, empagliflozin increased urinary citrate excretion by 60% in non-diabetic stone formers, irrespective of glycemia (19). This change correlated with reduced urinary supersaturation for calcium phosphate and uric acid, indicating a beneficial shift in stone risk.

Reduction in serum uric acid and increase in urate excretion

Sodium-glucose co-transporter 2 inhibitors lower serum uric acid levels primarily through increased renal excretion of urate, a mechanism that may involve inhibition of the GLUT9 transporter in the proximal tubule (19). Evidence from the SWEETSTONE trial indicates that empagliflozin was associated with a 30% reduction in the relative supersaturation of uric acid, even in the presence of increased uricosuria. These results suggest that urinary pH—rather than uric acid excretion per se—is the predominant determinant of uric acid stone risk in this context.

Modulation of urinary pH

The effects of SGLT2 inhibitors on urinary pH are multifactorial and reflect their influence on tubular transport, hormonal signaling, and systemic metabolism. Inhibition of the sodium-hydrogen exchanger NHE3 in the proximal tubule reduces hydrogen ion secretion and promotes bicarbonate retention, potentially contributing to a less acidic urinary milieu rather than a uniform alkalinization (20).

Additionally, these agents may raise circulating glucagon levels, which are known to impair bicarbonate reabsorption in the thick ascending limb of Henle's loop, further contributing to urinary alkalinization (21). From a metabolic perspective, SGLT2 inhibitors shift substrate utilization toward enhanced fatty acid oxidation and reduced ammoniagenesis, which in turn affects renal acid-base handling and can modulate urinary acidification (22).

These combined mechanisms were evident in the SWEETSTONE trial (Fig. 2), where urinary pH stabilized at approximately 5.6 across both calcium and uric acid stone formers. Notably, uric acid stone formers experienced a mild increase in urinary pH, while calcium-based stone formers showed a slight decline. These pH shifts were associated with substantial reductions in the relative supersaturation of calcium phosphate (by 36%) and uric acid (by 30%), reinforcing the relevance of SGLT2i-mediated pH modulation in altering lithogenic risk profiles (19).

Recent studies also suggest that patients with calcium oxalate stones may exhibit impaired net acid excretion due to subtle proximal tubular dysfunction, leading to persistently low urinary pH despite normal systemic acid–base balance (23). This altered acidification profile may contribute to reduced urinary citrate and increased lithogenic risk. SGLT2 inhibitors may help partially correct this defect by modulating tubular acid–base handling.

These observations further support the central role of urinary pH in modulating lithogenic risk. As emphasized by Khan et al. (12), even small shifts in urinary pH can significantly influence the crystallization of uric acid and calcium phosphate, reinforcing the clinical relevance of targeted pharmacological modulation of urinary acidification.

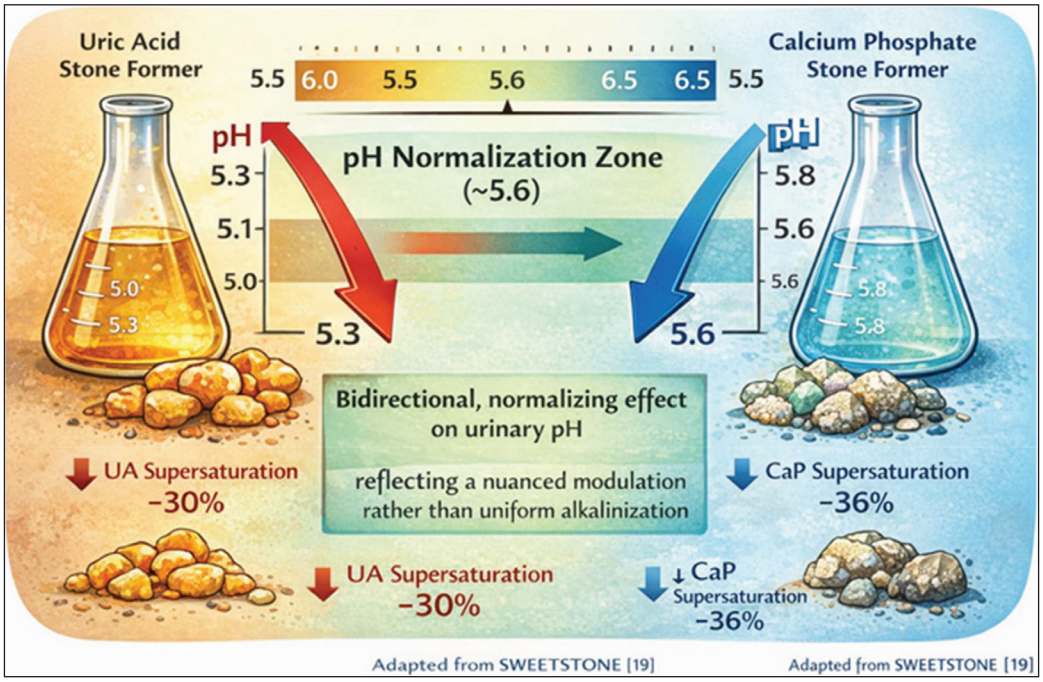

FIGURE 2 - Bidirectional modulation of urinary pH by empagliflozin. Empagliflozin stabilized urinary pH at approximately 5.6 across different stone phenotypes. The red arrow indicates a relative increase in urinary pH in uric acid stone formers, whereas the blue arrow reflects a mild reduction in urinary pH in calcium phosphate stone formers. These findings support a bidirectional, normalizing effect of SGLT2 inhibition on urinary acidification rather than a uniform alkalinizing action, with important implications for the reduction of lithogenic risk profiles. Adapted from Anderegg et al. (19)

Anti-inflammatory and tubuloprotective properties

Recent discoveries in the pathogenesis of kidney stone disease underscore the critical role of inflammation and immune activation in calcium oxalate stone formation, beyond simple urinary supersaturation and crystallization events (22,24).

Macrophages with pro-inflammatory M1 polarization, frequently observed near Randall's plaques, release reactive oxygen species and cytokines such as tumor necrosis factor-alpha and interleukin-1 beta, contributing to local injury and crystal adhesion (11-14). Dominguez-Gutierrez and colleagues demonstrated that calcium oxalate crystals can activate circulating monocytes and promote their differentiation into M1 macrophages, initiating a vicious cycle of inflammation and tissue damage that facilitates further crystal aggregation (13). These findings suggest that modulating the immune response may represent a novel therapeutic strategy to prevent kidney stones.

Sodium-glucose co-transporter 2 inhibitors have been shown to reduce inflammation and protect renal tubular structures in both diabetic and non-diabetic models. These agents lower the expression of inflammatory markers, preserve epithelial integrity, and improve the local immune environment (17,25).

In stone-forming conditions unrelated to diabetes, defective autophagy has been implicated in mitochondrial damage, oxidative stress, cytokine release, and structural injury to tubular epithelial cells. These alterations favor crystal retention and exacerbate inflammation.

Recent mechanistic studies suggest that sodium-glucose co-transporter 2 inhibitors restore autophagic activity, thereby mitigating tubular injury. In a non-diabetic mouse model of calcium oxalate nephrolithiasis, Liu and colleagues found that dapagliflozin reduced crystal-induced damage by restoring autophagy, decreasing oxidative stress, and suppressing activation of interleukin-1 beta and the NLRP3 inflammasome (26). These changes correlated with fewer crystal deposits, less tubular injury, and lower urinary levels of neutrophil gelatinase-associated lipocalin and interleukin-18, biomarkers of tubular inflammation.

A graphical summary of these mechanisms is shown in Figure 3 (26).

Khan and colleagues further emphasized that the inflammatory and oxidative milieu surrounding interstitial plaques plays a crucial role in initiating and sustaining epithelial injury. Thus, targeting these processes through pharmacologic means—such as sodium-glucose co-transporter 2 inhibitors—may offer a novel pathway to reduce lithogenic risk by preserving tubular health (12).

These findings support the concept that SGLT2 inhibitors may act upstream in the lithogenic cascade by stabilizing the tubular microenvironment and preventing crystal retention rather than merely altering urinary supersaturation.

Increased urinary volume

Although osmotic diuresis is a well-established effect of sodium-glucose co-transporter 2 inhibitors, the SWEETSTONE trial did not observe significant changes in 24-hour urine volume among normoglycemic stone formers. This finding suggests that the lithoprotective effects of SGLT2 inhibitors may not be primarily mediated by increased urine dilution in this population. Nonetheless, empagliflozin favorably influenced other urinary parameters, including higher citrate levels and reduced supersaturation of calcium phosphate and uric acid, suggesting benefits independent of diuresis (19,26) (see

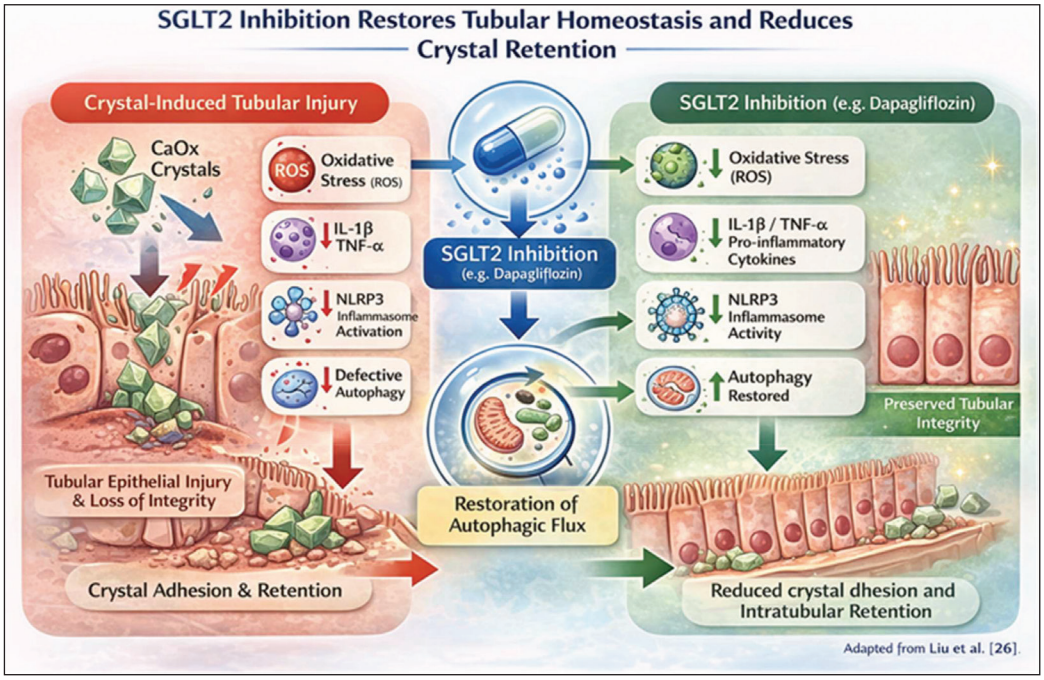

FIGURE 3 - Protection against crystal-induced renal injury. Schematic representation of the mechanisms by which SGLT2 inhibition mitigates calcium oxalate–induced tubular damage. Crystal deposition triggers oxidative stress, activation of the NLRP3 inflammasome, and pro-inflammatory cytokine release (e.g., IL-1β), leading to tubular epithelial injury and defective autophagy. SGLT2 inhibitors restore autophagic flux, reduce oxidative stress and inflammatory signaling, and preserve mitochondrial and tubular epithelial integrity. These effects translate into reduced crystal adhesion and intratubular retention, thereby attenuating lithogenic processes**.** Adapted from Liu et al. (26).

TABLE 1 - Effect of empagliflozin on urinary parameters in non-diabetic stone formers (adapted from SWEETSTONE (19)) . The reduction in lithogenic risk appears to be primarily driven by increased urinary citrate excretion and bidirectional normalization of urinary pH, rather than by changes in urine volume or isolated alterations in calcium excretion. Clinical implication: SGLT2 inhibitors may reduce stone risk through metabolic and tubular mechanisms independent of diuresis, supporting their potential role beyond conventional fluid-based prevention strategies.

Parameter	Calcium Stone Formers	Uric Acid Stone Formers
Relative Supersaturation (CaP)	↓ 36% **(significant)**	↓ 8% (not significant)
Relative Supersaturation (UA)	↓ 1% (not significant)	↓ 30% **(significant)**
Relative Supersaturation (CaOx)	↓ 32% (not significant)	↑ 8% (not significant)
Urinary pH	5.8 → 5.6	5.3 → 5.6
→ Convergence toward a common pH range (~5.6)	✔	✔
Urinary Citrate	↑ 60% **(significant)**	↑ 40% **(significant)**
→ Major driver of reduced lithogenic risk	✔	✔
Urinary Uric Acid	↑ 13%	↓ 7%
Urinary Calcium	↑ 23%	not significant
Urinary Oxalate	not significant	not significant
Urine Volume	not significant	not significant
→ No major contribution to lithoprotection	✔	✔
Net Acid Excretion (NAE)	↑ 26%	↓ 9%
Net GI Alkali Absorption	↑ 24%	↑ 7%

Table 1). These observations challenge the traditional paradigm that increased urine volume is the dominant protective mechanism in nephrolithiasis, highlighting a more complex metabolic and tubular modulation. A broader summary of the main mechanistic pathways potentially linking SGLT2 inhibition to reduced lithogenic risk is provided in Table 2.

SGLT2 inhibitors exert pleiotropic metabolic and renal effects extending beyond glycemic control, including modulation of tubular function, natriuresis, and systemic metabolic pathways (27). Emerging evidence also suggests a potential role in nephrolithiasis prevention through effects on urinary chemistry and tubular homeostasis (28).

TABLE 2 - Mechanistic rationale for the use of SGLT2 Inhibitors in nephrolithiasis prevention. SGLT2 inhibitors exert a multimodal effect on nephrolithiasis risk, acting on urinary chemistry, tubular function, and inflammatory pathways, with a convergent impact on crystal formation and retention. This table summarizes experimental and clinical findings supporting a mechanistic basis for SGLT2i effects on urinary factors and renal pathophysiology relevant to kidney stone formation.

Proposed Mechanism	Supporting Evidence	References
↑ Urinary citrate	Increased citrate excretion in SWEETSTONE and experimental models, linked to reduced supersaturation	(19)
Bidirectional modulation of urinary pH	Convergence toward ~5.6; small pH shifts affect CaP and UA crystallization	(19, 12)
↓ Serum uric acid	Increased renal urate excretion and reduced serum levels	(9, 19)
↓ CaP supersaturation	Significant reduction in calcium phosphate RSR in Ca stone formers	(19)
↓ UA supersaturation	Significant reduction in uric acid RSR in UA stone formers	(19)
Modulation of calcium handling	Indirect tubular effects; variable net impact	(18, 31, 32)
↓ Inflammation	Reduced cytokine signaling and inflammatory markers	(24, 25)
↑ Tubular protection	Restoration of autophagy, reduced oxidative stress and epithelial integrity	(26)
↓ Crystal retention	Reduced adhesion and intratubular retention	(26, 12)
↓ Oxidative stress	Reduced ROS and improved mitochondrial function	(25, 26)

Clinical evidence of SGLT2i in nephrolithiasis

The potential role of SGLT2i in NL prevention has gained momentum, driven by converging preclinical and clinical evidence. While their use in this context remains off-label, both randomized controlled trials and real-world data increasingly support a rationale for their therapeutic repositioning.

The SWEETSTONE trial: proof of concept in non-diabetic stone formers

The SWEETSTONE trial, conducted at the University Hospital of Bern, was the first randomized, double-blind, placebo-controlled crossover study specifically designed to assess the impact of SGLT2 inhibition on lithogenic urinary parameters in non-diabetic stone formers. The study enrolled 53 adults aged 18-75 years with a history of kidney stones composed of at least 80% calcium or uric acid. Participants received empagliflozin 25 mg once daily for two weeks, followed by a washout period and subsequent crossover.

The results demonstrated that empagliflozin significantly altered several lithogenic risk factors. Among calcium stone formers, a 36% reduction in calcium phosphate relative supersaturation (RSR) was observed, while uric acid stone formers experienced a 30% decrease in uric acid RSR. Urinary citrate excretion increased by approximately 60%, representing the most consistent and quantitatively relevant change across both groups, a change strongly associated with the filtered glucose load. Urinary pH stabilized around 5.6, with a slight rise in uric acid stone formers and a modest decrease in those forming calcium-based stones.

Importantly, these effects reflect a bidirectional normalization of urinary pH rather than a uniform alkalinizing action, consistent with the differential pathophysiology of calcium phosphate and uric acid stone formation (Fig. 2).

Notably, these improvements occurred independently of significant changes in urinary volume, supporting the concept that SGLT2 inhibitors exert lithoprotective effects primarily through metabolic and tubular mechanisms rather than through osmotic diuresis alone.

These findings support the hypothesis that SGLT2 inhibitors can beneficially modulate urinary risk factors for nephrolithiasis even in normoglycemic individuals (19)**.** Importantly, these interventional findings are based on empagliflozin, and extrapolation to other SGLT2 inhibitors should therefore be made with caution. Nevertheless, the concordant direction of effect observed in observational studies across the class suggests that at least part of the benefit may reflect a broader class effect.

They also align with mechanistic models proposed by Khan et al., wherein modification of urinary biochemistry—such as increased citrate and pH modulation—could prevent crystal adherence and growth in the renal papilla and tubules, thus interrupting the cycle of Randall's plaque formation and calcium oxalate stone development (12).

Taken together, these findings position SGLT2 inhibition as a potential upstream intervention in the lithogenic cascade, targeting early metabolic and tubular determinants of stone formation.

Clinical implementation and practical considerations

In clinical practice, the use of sodium–glucose co-transporter 2 inhibitors in stone formers must be guided by individual metabolic profiles, comorbid conditions, and risk stratification. These agents may be particularly advantageous in patients presenting with hypocitraturia, low urinary pH, hyperuricemia, or those with coexisting type 2 diabetes mellitus, chronic kidney disease, or metabolic syndrome. These conditions are frequently associated with increased lithogenic risk and may be favorably modulated by the pleiotropic effects of SGLT2 inhibitors (19,26-29).

Several considerations are relevant to their implementation:

First, renal function and volume status should be closely monitored, particularly in elderly individuals, patients concurrently using diuretics, or those with stage 3 or higher chronic kidney disease. Initiation of SGLT2 inhibitors may lead to a transient decline in estimated glomerular filtration rate and mild volume contraction (30).

Second, although urinary calcium excretion may increase modestly with certain agents—such as canagliflozin—the concomitant rise in urinary citrate and modulation of urinary pH may counterbalance the associated lithogenic risk. Baseline 24-hour urine testing is advisable, especially in patients with a history of hypercalciuria. Importantly, current evidence suggests that changes in calcium handling are variable and not the primary driver of lithogenic risk modification. Moreover, while SGLT2 inhibitors can influence bone and mineral metabolism by altering calcium and phosphate handling, the net lithogenic impact appears to be mitigated by concurrent metabolic effects (31,32).

Third, regarding tolerability and safety, concerns about urinary tract infections related to glycosuria have emerged. However, recent meta-analyses indicate only a modest increase in infection risk (33,34). Educating patients on personal hygiene and maintaining adequate hydration remains crucial. It is also important to avoid SGLT2 inhibitors in individuals with a history of diabetic ketoacidosis or significant dehydration.

Finally, the use of SGLT2 inhibitors should be integrated into a broader strategy of stone prevention, encompassing dietary adjustments, fluid intake optimization, and correction of urinary biochemical abnormalities. Rather than replacing conventional therapies, SGLT2 inhibitors should be considered as an adjunctive, mechanism-based intervention in selected high-risk patients. A phenotype-driven approach, based on urinary biochemical profiles, may help identify patients most likely to benefit from SGLT2 inhibition.

Observational evidence in diabetic populations

Patients with metabolic syndrome and type 2 diabetes mellitus represent a high-risk phenotype for nephrolithiasis, due to a constellation of lithogenic abnormalities such as low urinary pH, hyperuricosuria, and hypocitraturia. These metabolic derangements create a permissive urinary environment for stone formation, especially uric acid and mixed stones (12).

Beyond interventional trials, several large-scale observational studies have examined the incidence of nephrolithiasis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors. In a multicenter cohort study, the use of SGLT2 inhibitors was associated with a ~30% reduction in the risk of incident kidney stones (HR ~0.69-0.74) (34).

Additionally, a target trial emulation study reported a reduction in recurrent nephrolithiasis risk (RR ~0.67-0.73) (35) among patients treated with SGLT2 inhibitors compared with GLP-1 receptor agonists or DPP-4 inhibitors.

Furthermore, meta-analytic data indicate a consistent protective signal, with pooled estimates suggesting a ~35-40% reduction in nephrolithiasis risk (OR ~0.61-0.66) (36) across large populations.

Although residual confounding cannot be excluded, these consistent findings across heterogeneous cohorts strengthen the hypothesis that SGLT2 inhibitors may exert protective effects against stone formation in metabolically vulnerable populations. Importantly, the concordance between observational findings and mechanistic data further supports a biologically plausible effect.

Such protection may be mediated through correction of urinary biochemical abnormalities and attenuation of renal inflammation.

A structured summary of the most relevant recent clinical and preclinical studies is provided in Table 3.

The table reports key characteristics of the most relevant studies, including study design, population, type of SGLT2 inhibitor used, comparator group, definition of stone-related outcomes, and the main effect estimates. Both interventional

TABLE 3 - Summary of recent clinical and preclinical evidence evaluating the association between sodium–glucose cotransporter-2 inhibitors and nephrolithiasis risk (2022-2025)

First Author	Year	Journal	Study Type	Population	Outcome	Effect	Ref
Paik	2024	JAMA Intern Med	Cohort study	T2D patients	Incident nephrolithiasis	Lower risk (HR ~0.69-0.74)	**(34)**
Sakhaee	2024	BMJ	Target trial emulation	T2D + prior stones	Recurrent nephrolithiasis	Reduced risk (RR ~0.67-0.73)	**(35)**
Kanbay	2025	Nephrol Dial Transplant	Meta-analysis	Large cohorts	Nephrolithiasis	OR ~0.61-0.66	**(36)**
Yeh	2025	Diabetes Res Clin Pract	Cohort/meta-analysis	T2D patients	Incident nephrolithiasis	Reduced risk	**(30)**
Anderegg	2025	Nature Medicine	RCT (crossover)	Non-diabetic stone formers	Supersaturation	↓ CaP & UA RSR	**(19)**
Liu	2025	EBioMedicine	Preclinical study	Animal model	Crystal deposition	Reduced stone burden	**(26)**

and real-world observational studies are included. Evidence across large administrative cohorts consistently supports a reduced risk of incident or recurrent nephrolithiasis in patients treated with SGLT2 inhibitors compared with GLP-1 receptor agonists, DPP-4 inhibitors, or placebo. The SWEET-STONE randomized, double-blind, crossover trial provides the first interventional proof-of-concept in non-diabetic stone formers, demonstrating significant reductions in relative supersaturation of calcium phosphate and uric acid. Preclinical models show concordant reductions in crystal deposition. Overall, the consistency of findings across mechanistic, interventional, and observational studies strengthens the biological plausibility of a protective effect of SGLT2 inhibitors against nephrolithiasis.

These findings, while not definitive, provide consistent real-world support for the hypothesis generated by interventional and mechanistic studies.

Mechanistic translation and clinical relevance

The convergence of pleiotropic effects—such as enhanced urinary citrate excretion, improved urinary pH balance, reduced serum uric acid, and anti-inflammatory properties—offers a strong mechanistic rationale for the use of SGLT2 inhibitors in nephrolithiasis (10,17,19,24,26). Importantly, these effects appear largely independent of glycemic control, broadening the therapeutic applicability of these agents to non-diabetic stone formers as well.

SGLT2 inhibitors intervene at multiple levels of the lithogenic cascade. In particular, they may mitigate epithelial damage, oxidative stress, and inflammatory activation—key contributors to Randall's plaque formation and calcium oxalate stone anchoring, as described by Khan et al. (12).

Recent studies also highlight the ability of SGLT2 inhibitors to restore cellular homeostasis in the renal tubule. Through modulation of autophagy and suppression of the NLRP3 inflammasome, these agents could stabilize the intrarenal environment and reduce crystal adhesion and retention (26).

Taken together, these mechanisms suggest that SGLT2 inhibitors may act upstream in the lithogenic cascade, targeting early tubular and metabolic determinants of stone formation rather than solely modifying urinary supersaturation.

Therefore, SGLT2 inhibitors emerge not merely as metabolic modulators, but as potential nephroprotective agents with the ability to disrupt key events in the stone pathogenesis continuum—offering a rationale for their integration into tailored prevention strategies in high-risk patients (19,26,28).

This integrative effect across metabolic, tubular, and inflammatory pathways distinguishes SGLT2 inhibition from conventional stone prevention strategies, which typically target single urinary parameters**.**

Several practical considerations should be addressed in clinical practice (Table 4).

Clinical applications: positioning SGLT2i in stone prevention

Although not formally approved for nephrolithiasis, SGLT2 inhibitors offer promising preventive potential across several clinical scenarios (Fig. 4). In individuals with type 2 diabetes or diabetic kidney disease, these agents may correct common lithogenic abnormalities—such as acidic urine, low citrate, and hyperuricemia—while providing established cardiovascular and renal benefits (19,35).

Patients with idiopathic or secondary hypocitraturia, including those with distal renal tubular acidosis (dRTA), polycystic kidney disease (PKD), or cystinuria (37), may also benefit. In such settings, SGLT2 inhibitors can increase urinary citrate without inducing excessive alkalinization, an advantage for calcium phosphate stone formers (19).

They may also be useful in patients who do not tolerate or respond to conventional therapies like potassium citrate or thiazides (28). Their modest diuretic and metabolic effects on urinary citrate and pH may reduce urinary supersaturation while avoiding excessive calciuria (31,32).

TABLE 4 - Practical considerations for SGLT2i use in stone formers. Patient selection should ideally be guided by urinary metabolic profiling to identify those most likely to benefit from SGLT2 inhibition.

Domain	Considerations
Renal Function and Volume	Monitor eGFR and fluid status, especially in older patients, those on diuretics, or with stage ≥3 CKD. Initiation of SGLT2 inhibitors may lead to a transient decline in eGFR and mild volume contraction (30).
Calcium Handling and Mineral Balance	Mild increases in urinary calcium may occur (notably with canagliflozin), but concurrent increases in urinary citrate and modulation of urinary pH may mitigate lithogenic risk. Baseline 24-hour urine evaluation is advisable in hypercalciuric patients (31,32).
Urinary Chemistry	Favorable changes in urinary citrate and bidirectional modulation of urinary pH represent the dominant mechanisms of lithogenic risk reduction, rather than changes in urine volume.
Tolerability and Safety	Slightly increased risk of genital or urinary tract infections; patient education on hygiene and hydration is recommended. Avoid use in individuals with a history of diabetic ketoacidosis or significant volume depletion (33,34).
Therapeutic Integration	Use within a comprehensive prevention strategy, including diet, hydration, and correction of urinary abnormalities. SGLT2 inhibitors should be considered as an adjunctive, mechanism-based therapy in selected high-risk patients rather than a replacement for conventional treatments.

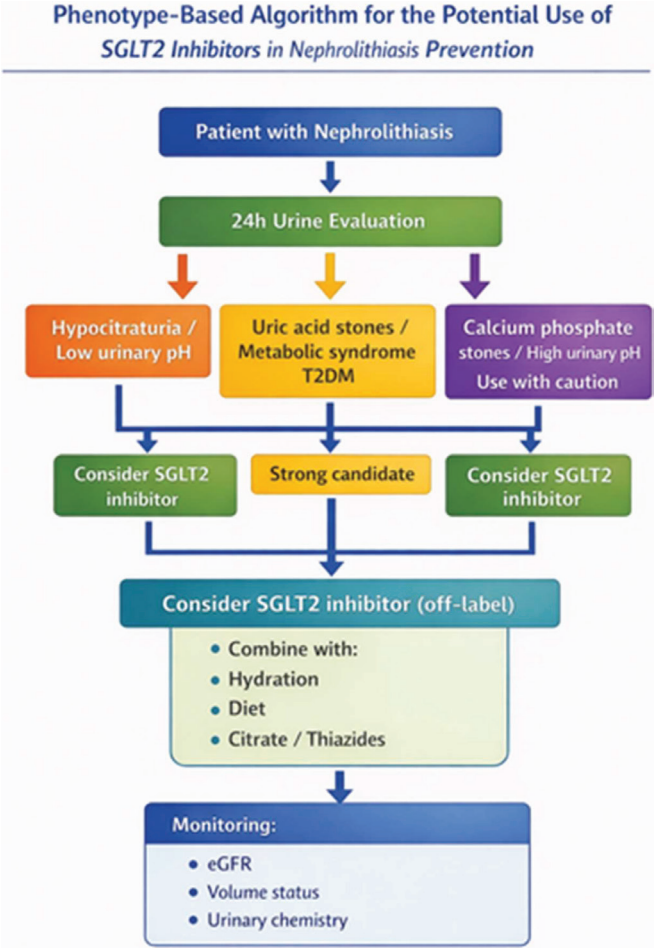

FIGURE 4 - Suggested algorithm for the potential off-label use of SGLT2 inhibitors in nephrolithiasis prevention.

Importantly, these potential applications should be interpreted within a phenotype-driven framework, based on individual urinary biochemical profiles and underlying metabolic abnormalities.

These emerging applications support the need for prospective trials targeting stone recurrence as a primary outcome and highlight the relevance of individualized preventive strategies guided by underlying metabolic patterns.

This phenotype-based algorithm outlines clinical scenarios in which SGLT2 inhibitors may be considered as adjunctive therapy. Candidate patients include those with hypocitraturia, low urinary pH, uric acid stones, or metabolic comorbidities such as type 2 diabetes and chronic kidney disease.

Additional conditions, such as distal renal tubular acidosis, polycystic kidney disease, and cystinuria, may also represent potential targets based on shared metabolic features.

The algorithm emphasizes integration with standard preventive measures, including hydration, dietary modification, and correction of urinary abnormalities, as well as careful monitoring of renal function and volume status.

Limitations and future directions

Most clinical evidence for SGLT2 inhibitors in stone prevention stems from short-term studies or observational analyses, with kidney stones often reported as secondary outcomes. The SWEETSTONE trial provided essential proof of concept, but its sample size and duration remain limited (19). Furthermore, data from non-diabetic populations remain scarce, despite similar pathophysiologic targets.

Mechanistic findings—while promising—largely originate from preclinical models. Their translation into clinically meaningful outcomes in humans remains to be fully established. Future validation in humans should include biomarker studies, imaging of papillary changes, and functional tubular assays. Table 5 summarizes key considerations for integrating SGLT2i into clinical stone prevention protocols.

This table summarizes patient phenotypes that may derive particular benefit from SGLT2 inhibitor therapy based on shared metabolic features and mechanistic plausibility. Proposed rationales include improvements in urinary pH, citrate, and uric acid handling; reduction of acid load; and mechanisms independent of calcium excretion.

Although SGLT2 inhibitors are not currently approved for kidney stone prevention, emerging clinical and mechanistic evidence suggests a potential role in selected high-risk subgroups, including patients with diabetes, hypocitraturia, incomplete distal renal tubular acidosis, intolerance to conventional therapies, and non-diabetic recurrent calcium phosphate or uric acid stone formers.

TABLE 5 - Potential clinical applications of sodium–glucose cotransporter-2 inhibitors in nephrolithiasis prevention

Patient Profile	Rationale for Use
T2DM or diabetic kidney disease	Correction of low urinary pH, hypocitraturia, and hyperuricemia; established cardio-renal benefits
Idiopathic or secondary hypocitraturia	An increase in urinary citrate represents a key anti-lithogenic mechanism
Incomplete dRTA	Potential normalization of urinary acidification and citrate excretion
Intolerance to thiazides or potassium citrate	Alternative mechanism-based option without reliance on alkalinization or calcium modulation alone
Non-diabetic recurrent CaOx or uric acid stone formers	Mechanism-driven approach supported by emerging interventional and observational evidence

These proposed applications should be considered hypothesis-generating and interpreted in the context of currently available evidence, which remains limited for stone-specific outcomes.

Conclusion and research priorities

SGLT2 inhibitors represent a promising new avenue in nephrolithiasis prevention. By modulating multiple lithogenic pathways—including urinary citrate, uric acid, pH, and inflammation—they address the multifactorial pathogenesis of stone disease. Early data support their use in both diabetic and non-diabetic patients, especially those with hypocitraturia, acidic urine, or other metabolic risk traits, including those with distal renal tubular acidosis (dRTA), polycystic kidney disease (PKD), or cystinuria (37).

Importantly, their effects appear to extend beyond simple changes in urinary volume, reflecting a broader impact on tubular function, metabolic homeostasis, and inflammatory pathways.

Further research is needed to define optimal indications, patient selection, and long-term efficacy. In particular, the absence of randomized trials with stone recurrence as a primary endpoint remains a key limitation. Future studies should also clarify whether the observed lithoprotective effects represent a true class effect or whether clinically relevant heterogeneity exists among individual SGLT2 inhibitors.

Key priorities include large, multicenter trials powered to assess recurrence, mechanistic studies targeting tubular health and inflammation, and cost-effectiveness analyses. These efforts should aim to incorporate SGLT2 inhibitors into precision nephrology frameworks, enabling individualized prevention strategies based on patient-specific metabolic profiles (38).

Conclusive Box: Key Takeaways

- SGLT2 inhibitors increase urinary citrate and promote bidirectional normalization of urinary pH, reducing lithogenic risk.
- They lower serum uric acid and reduce uric acid supersaturation.
- Their effects appear to be independent of urine volume, reflecting broader metabolic and tubular mechanisms.
- They may benefit both diabetic and non-diabetic stone formers, particularly those with hypocitraturia or acidic urine.
- Current evidence is promising but remains limited; dedicated trials with stone recurrence endpoints are needed.

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