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REVIEW
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SGLT2 inhibitors in the prevention of nephrolithiasis: a comprehensive review

Marco Lombardi[1], Pamela Gallo[1], Selene Laudicina[1], Lisa Buci[2], Francesco Giudici[3], Alfonso Baldoncini[4], Simone Agostini[5], Alfonso Crisci[6], Stefano Michelassi[1]

[1]Nephrology and Dialysis Unit, Santa Maria Annunziata Hospital, ASL Toscana Centro, Florence -Italy
[2]Endocrinology Unit, AOU Careggi Hospital, Florence - Italy
[3]Department of Clinical and Experimental Medicine, University of Florence, Florence - Italy
[4]Nuclear Medicine Unit, ASL Toscana Sud Est, Arezzo - Italy
[5]Department of Emergency and Urgency Radiology, Careggi University Hospital, Florence - Italy
[6]Oncologic Minimally Invasive Urology and Andrology Unit, Department of Experimental and Clinical Medicine, Careggi Hospital, University of Florence, Florence - Italy

ABSTRACT

Nephrolithiasis (NL) is frequently associated with metabolic disorders such as type 2 diabetes mellitus (T2DM), obesity, and chronic kidney disease (CKD), all of which alter urinary composition and increase the risk of calcium oxalate and uric acid stone formation. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), originally developed for glycemic control in T2DM, have emerged as promising agents with both renoprotective and anti-lithogenic effects. These effects are mediated through mechanisms such as osmotic diuresis, increased urinary citrate excretion (citraturia), and modulation of urinary pH, all contributing to reduced supersaturation and stone risk. This review provides a comprehensive overview of the mechanisms by which SGLT2i may prevent stone formation, alongside a critical analysis of the current clinical evidence.

Keywords: Citraturia, Nephrolithiasis, SGLT2 inhibitors, Supersaturation, Type 2 diabetes mellitus, Urinary pH

Introduction

Nephrolithiasis (NL) is increasingly recognized as a systemic condition rather than a merely urological disorder. Several epidemiological studies have demonstrated a higher prevalence of arterial hypertension (1), obesity (2), diabetes mellitus (T2DM) (3), gout and dyslipidemia (4), cardiovascular disease (5), chronic kidney disease (CKD) (6), and low bone mineral density (7) among kidney stone formers.

Stone formation occurs when urinary concentrations of lithogenic solutes exceed their solubility thresholds, a condition known as supersaturation. Relative supersaturation ratios (RSR) for calcium oxalate (CaOx), calcium phosphate (CaP), and uric acid (UA) serve as reliable surrogate markers for the risk of stone recurrence. Supersaturation of urine with calcium, oxalate, phosphate, and uric acid promotes crystallization, especially in the context of reduced urinary volume and altered urinary pH (8). The rising incidence of NL over recent decades has paralleled the increasing prevalence of T2DM, obesity, and metabolic syndrome, likely due to the impact of these conditions on urinary biochemistry and pH (9).

Insulin resistance, the shared pathophysiological basis of these metabolic disorders, is closely associated with decreased urinary pH, mainly due to impaired renal ammoniagenesis (10,11). The acidification of the urinary milieu contributes to hypocitraturia by shifting citrate from its trivalent to divalent form (from $citrate^{3-}$ to $citrate^{2-}$), the latter being preferentially reabsorbed by the sodium-dicarboxylate co-transporter NaDC1 (12,13). Concurrently, compensatory hyperinsulinemia may enhance urinary calcium excretion (14-16). The combination of low urinary pH, hypercalciuria, and hypocitraturia establishes a pro-lithogenic urinary environment that favors the formation of both CaOx and UA stones (9,17,18).

The well-established association between T2DM and NL has led to growing interest in SGLT2i as potential NL-modifying agents. SGLT2i target the sodium-glucose co-transporter isoform 2 (SGLT2), encoded by the *SLC5A2* gene, which is predominantly expressed in the brush-border membrane of proximal tubular cells, where it facilitates reabsorption of approximately 90% of filtered glucose (19-21).

Although early observations suggested that SGLT2i might increase the risk of kidney stone formation due to their uricosuric effect and potential for lowering urinary pH (22),

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Corresponding author:
Marco Lombardi
email: lombardim969@gmail.com

subsequent evidence has instead revealed a protective role; in fact, as early as 2009, dapagliflozin was patented with the prevention of NL listed among its indications (23). In a large observational study comparing SGLT2i and GLP-1 receptor agonists in patients with T2DM, Kristensen et al. reported a significantly reduced risk of both incident (HR 0.51, 95% CI 0.37-0.71) and recurrent (HR 0.68, 95% CI 0.48–0.97) NL in the SGLT2i group (24). More recently, a meta-analysis of randomized clinical trials demonstrated that empagliflozin was associated with an approximate 40% reduction in urinary tract stone events among patients with T2DM (25).

This review aims to explore the physiological mechanisms by which SGLT2i may reduce the risk of NL, critically examining the available experimental and clinical data supporting their use in NL prevention.

Increased Urinary Flow

SGLT2i promote osmotic diuresis, which may contribute to NL prevention by reducing the urinary concentration of lithogenic solutes (15). However, the effect of SGLT2i on sodium and water excretion is variable and depends on the underlying clinical context.

In individuals with normal baseline tubular sodium reabsorption—such as healthy subjects or patients with compensated T2DM—SGLT2i typically cause an acute increase in urinary sodium, glucose, and water excretion (26-31). Conversely, in clinical settings characterized by avid sodium retention—such as in patients with heart failure, particularly during acute decompensation—SGLT2 inhibition leads predominantly to glycosuria-induced osmotic diuresis, with increased free water clearance and minimal changes in natriuresis (32-35).

Nonetheless, both the initial natriuretic and osmotic effects of SGLT2i are rapidly attenuated by compensatory mechanisms: sodium reabsorption is enhanced distally in response to effective hypovolemia, while water conservation is triggered by activation of the thirst mechanism and antidiuretic hormone release. As a result, natriuresis tends to be transient, whereas glucosuria persists, indicating a lack of pharmacological tolerance at the proximal tubule level. Despite the attenuation of diuresis over time, SGLT2i continue to exert favorable effects on stone prevention.

Importantly, the benefit of SGLT2i in reducing stone risk extends beyond simple volume expansion. In the SWEETSTONE trial—a randomized, double-blind, placebo-controlled crossover study investigating the effect of empagliflozin in non-diabetic adults—empagliflozin improved urinary lithogenic parameters even without a significant increase in urinary volume (36,37). This finding confirms that the antilithogenic effects of SGLT2i are not solely dependent on diuresis.

In clinical practice, it is challenging to quantify the specific contribution of pharmacologically induced diuresis to stone prevention, particularly because high fluid intake is universally recommended to all patients with a history of NL. This confounds the ability to isolate the incremental effect of SGLT2i-induced urinary flow in this population.

Effects of SGLT2 Inhibitors on Uric Acid and Urine pH

SGLT2i reduce serum uric acid concentrations and have been associated with a decreased risk of gout (38), likely through inhibition of tubular urate reabsorption via both the apical URAT1 and basolateral GLUT9 transporters (22). Although hyperuricosuria could theoretically promote UA stone formation, it is well established that low urinary pH—rather than elevated uric acid excretion—is the principal driver of uric acid stone pathogenesis (39).

In patients with T2DM, UA stones are more prevalent than in non-diabetic individuals (36% vs 11%, respectively), primarily due to insulin resistance-associated acidification of urine (9). So, the effect of SGLT2i on urinary pH becomes a critical point—but the evidence remains inconclusive.

Studies have yielded conflicting results regarding the impact of SGLT2i on urinary pH, with some reporting an increase in urine pH (40-42) and others a decrease (43). A key element in this regulatory mechanism is the sodium–hydrogen exchanger isoform 3 (NHE3), located on the apical membrane of proximal tubular cells and in the thick ascending limb of Henle's loop. NHE3 facilitates sodium reabsorption in exchange for H^+ or NH_4^+ ions, contributing to bicarbonate reabsorption: for each proton secreted, one bicarbonate moiety is reclaimed.

SGLT2 and NHE3 are structurally colocalized in the proximal tubule and functionally interlinked (22,44). Inhibition of SGLT2 may lead to reduced NHE3 activity, resulting in decreased H^+ and NH_4^+ secretion and thus potentially increasing urinary pH. However, this effect is far from consistent. In murine models, acute administration of empagliflozin led to a slight increase in urinary pH, whereas chronic exposure was paradoxically associated with a lowering of urinary pH (45), despite enhanced ammoniagenesis. One plausible explanation is a shift in metabolic energetic substrate utilization, with increased reliance on fatty acids and ketone bodies, leading to enhanced endogenous acid production (37,46).

The SWEETSTONE trial provided particularly nuanced insights into this issue. In this randomized controlled crossover study, empagliflozin induced differential pH responses in patients depending on the stone type. Specifically, it increased urinary pH in uric acid stone formers (from 5.3 to 5.6) and decreased it in calcium stone formers, thereby stabilizing urine pH at 5.6 across groups. Since low urinary pH is the major lithogenic factor in UA stones, and high urinary pH promotes CaP stone formation, this "clamping effect" on pH may optimize RSR for both stone types (37).

Effects of SGLT2 Inhibitors on Citrate

Citrate is a key urinary inhibitor of calcium stone formation, as it binds to calcium and reduces the availability of free calcium ions for crystal aggregation. Recent studies have shown that SGLT2i significantly increase urinary citrate excretion, with reported rises of up to 50% in both healthy volunteers and patients with T2DM (37,43,47,48). Scherr et al. (49) also documented increased urinary citrate levels following dapagliflozin administration in a patient with distal renal tubular acidosis secondary to tubulointerstitial nephritis.

Interestingly, while increases in urinary citrate typically correlate with higher urine pH, this is not consistently observed with SGLT2i. Empagliflozin has been shown to enhance urinary citrate excretion even in the presence of a reduction in urine pH (43). Similarly, dapagliflozin was associated with increased urinary citrate alongside a non-significant trend toward lower urinary pH (50).

A strong positive correlation between urinary citrate and filtered glucose load has been reported (37), suggesting a proximal tubular mechanism linking the handling of these two solutes. One hypothesis is that SGLT2i may inhibit citrate reabsorption by downregulating the activity of the sodium-dicarboxylate co-transporter 1 (NaDC1) in the proximal tubule. This effect may be mediated by indirect interactions involving scaffolding proteins such as MAP17, which has been shown to physically link SGLT2 to other transport systems, including NHE3 (22,44).

An alternative explanation involves the intracellular metabolism of citrate. SGLT2 inhibition may reduce the activity of cytosolic ATP citrate lyase, an enzyme that converts citrate into acetyl-CoA and oxaloacetate, thereby increasing intracellular citrate levels and decreasing its reabsorption via the basolateral membrane, ultimately leading to enhanced urinary excretion.

Regardless of the underlying mechanism, the increase in urinary citrate represents a potentially important anti-lithogenic effect of SGLT2i, particularly in patients with baseline hypocitraturia.

Effects of SGLT2 Inhibitors on Bone and Calcium-Phosphate Metabolism

SGLT2i have been associated with adverse skeletal effects. Specifically, canagliflozin and dapagliflozin have been linked to an increased risk of fractures (51). Canagliflozin has been shown to alter bone turnover markers, including elevated serum levels of fibroblast growth factor 23 and parathyroid hormone (52). In contrast, empagliflozin does not appear to share these effects, as no significant changes in bone biomarkers or fracture risk have been observed in multiple clinical studies (53,54).

From a renal perspective, SGLT2i increase urinary calcium excretion while reducing urinary phosphate excretion (55). Despite this, data from the SWEETSTONE trial demonstrated that empagliflozin treatment led to a 36% reduction in the RSR for CaP and had no significant impact on CaOx RSR, even though urinary calcium increased by 23% (37).

This paradox may be explained by the key role of brushite supersaturation in the pathogenesis of both CaP and CaOx stones. Interstitial CaP deposits—primarily hydroxyapatite—at the tip of renal papillae, known as Randall's plaques, act as nucleation sites for CaOx crystals (56-59). These plaques promote heterogeneous nucleation and the growth of apatite and other non-brushite CaP phases (60-62). Conversely, CaP stones themselves often originate as intratubular plugs, primarily composed of brushite or carbonate apatite, that obstruct the ducts of Bellini and eventually extend into the urinary collecting system (63).

Interestingly, the combined effect of increased urinary citrate and reduced urine pH observed in CaP stone-formers treated with SGLT2i may represent a class-specific protective mechanism. This is in stark contrast to alkali therapy (e.g., potassium citrate), which increases urinary citrate but also raises urine pH, potentially worsening CaP supersaturation. Therefore, SGLT2i may offer a unique therapeutic advantage in patients with calcium phosphate stones by dissociating citraturia from urinary alkalinization (37).

Other Potential Mechanisms

Beyond their direct metabolic effects, SGLT2i may exert a range of pleiotropic actions that could contribute to NL prevention. It has been hypothesized that, by promoting sustained water and energy loss, SGLT2i trigger metabolic adaptations similar to those observed in estivating animals—a state of dormancy characterized by decreased metabolic activity and efficient redistribution of endogenous resources (64). These adaptations are associated with reduced oxidative stress and may confer organ-level cytoprotection.

Additional proposed benefits of SGLT2i include anti-inflammatory effects, attenuation of tubulointerstitial fibrosis, and reduced oxidative stress, as well as downregulation of osteopontin expression, a molecule critically involved in crystal adhesion and aggregation within renal tubules (65-68). These mechanisms, though not specific to lithogenesis, intersect with key pathways involved in the development of kidney stones and may contribute to a more favorable intrarenal environment.

Moreover, by improving insulin sensitivity, SGLT2i may indirectly stimulate renal ammoniagenesis, potentially correcting the low urinary pH observed in insulin-resistant states such as type 2 diabetes and metabolic syndrome (69). This effect would complement their known actions on urinary citrate and glucose handling, reinforcing their anti-lithogenic potential.

Conclusion

Recent evidence strongly supports the role of SGLT2i in reducing the risk of NL. In patients with T2DM, these agents have been associated with an approximate 36% reduction in stone events (25), while in broader populations, risk reductions ranging from 26% to 49% have been reported (24,47,69). Notably, non-diabetic males and Japanese patients with T2DM treated with SGLT2i demonstrate lower rates of stone recurrence compared to those receiving other antidiabetic therapies (67).

These findings suggest that the clinical indications for SGLT2i—already extended beyond glycemic control to encompass cardiovascular and renal protection (70)—could reasonably be expanded to include NL prevention. Among the agents in this class, empagliflozin may offer specific benefits in patients predisposed to CaP stones, due to its ability to modulate both urinary citrate and pH without promoting phosphate supersaturation (37).

Nevertheless, further high-quality studies, including randomized controlled trials, are warranted to confirm the long-term efficacy of SGLT2i across different stone phenotypes and to clarify the underlying pathophysiological mechanisms that mediate their protective effects.

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