SGLT2i: The New Wonder Drugs for Kidney Stone Prevention?

By Amy A. Yau and David S. Goldfarb

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are cardio- and renal-protective in patients with heart failure and proteinuric kidney disease. However, Paik and colleagues' newest work (1) suggests that SGLT2i may also help prevent kidney stones (or nephrolithiasis). In their retrospective analysis of over 700,000 adults with type 2 diabetes, new users of SGLT2i had a lower incidence of kidney stones compared with new users of glucagon-like peptide-1 receptor antagonists (GLP-1RA) or dipeptidyl peptidase 4 inhibitors (DPP4i). Kidney stone events were 14.9 events per 1000 person-years in the patients treated with SGLT2i compared with 21.3 events per 1000 person-years in patients treated with GLP-1RA or DPP4i at an average of 192 days. Paik and colleagues' findings (1) are similar to other studies, which also found reduced odds and reduced incidence of kidney stones in patients treated with SGLT2i (2–4). However, these studies are all retrospective, in which glucose-lowering therapy was initiated for the usual indications and not for stone prevention.

Paik and colleagues' findings (1), although exciting, present more questions than answers. It is unclear whether SGLT2i are protective against all kidney stone types, if the effects are transferrable to stone formers who are nondiabetic, and what the underlying mechanisms might be. Interestingly, there was initial concern that SGLT2i could increase urinary stone formation. In healthy adults and rats treated with SGLT2i, urinary calcium increased (5). However, urine calcium excretion was not increased in healthy volunteers treated with empagliflozin (6). Urinary citrate increased by up to 18% in both healthy volunteers and patients with type 2 diabetes treated with SGLT2i, which may or may not have mitigated against any increase in urinary calcium (6, 7). Healthy volunteers treated with empagliflozin did have a reduced relative supersaturation rate (calculated by the EQUIL2 algorithm) of calcium phosphate, specifically brushite and hydroxyapatite, with no change in that of calcium oxalate. The role of urine citrate and reduced brushite saturation may be important, as brushite crystals are considered to be the nidus of most calcium kidney stones (8). Increases in urinary citrate are the most widely suggested mechanism for stone prevention in patients treated with SGLT2i, but the mechanism by which this effect occurs remains uncertain.

SGLT2i may be more important in the prevention of uric acid kidney stones given that uric acid stones are more common in stone formers who are diabetic (9). Increases in urine bicarbonate and urine pH occurred in mice treated with empagliflozin due to reduced sodium-hydrogen exchanger 3 activity and increased glutamine-mediated ammoniagenesis (10). Although SGLT2i are also uricosuric, uric acid stone formation is more dependent on low urine pH than on high urine uric acid levels (11). Yet, in healthy adults treated with empagliflozin, there was a trend toward lower urine pH with a higher relative supersaturation rate for uric acid (6). This effect was surprising and unexplained given that treatment was also associated with an increase in citrate excretion, a circumstance usually accompanied by increased urine pH.

Other possible mechanisms for stone prevention in individuals treated with SGLT2i include other unmeasured effects in the urine such as reduced inflammatory markers and kidney stone matrix proteins like osteopontin and albumin (1, 2). What is not accounted for are changes in patients' metabolic profile and weight, which can affect urine pH (7, 9). A final suggested mechanism is increased urinary flow, reducing kidney stone risk, but these effects are transient (2, 3). At this time, the findings from Paik et al. (1) are more thought-provoking than anything else, and we eagerly anticipate further studies to better identify target patient populations, large studies examining changes in urinary profiles, and comparisons of SGLT2i with standard preventative therapies. ■

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References

1. Paik JM, et al. Sodium-glucose cotransporter 2 inhibitors and nephrolithiasis risk in patients with type 2 diabetes. *JAMA Intern Med* 2024; 184:265–274. doi: 10.1001/jamainternmed.2023.7660
2. Anan G, et al. Inhibition of sodium-glucose cotransporter 2 suppresses renal stone formation. *Pharmacol Res* 2022; 186:106524. doi: 10.1016/j.phrs.2022.106524
3. Kristensen KB, et al. Sodium–glucose cotransporter 2 inhibitors and risk of nephrolithiasis. *Diabetologia* 2021; 64:1563–1571. doi: 10.1007/s00125-021-05424-4
4. Cosentino C, et al. Nephrolithiasis and sodium-glucose co-transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials. Diabetes *Res Clin Pract* 2019; 155:107808. doi: 10.1016/j.diabres.2019.107808
5. Cianciolo G, et al. Mineral and electrolyte disorders with SGLT2i therapy. *JBMR Plus* 2019; 3:e10242. doi: 10.1002/jbm4.10242
6. Harmacek D, et al. Empagliflozin changes urine supersaturation by decreasing pH and increasing citrate. *J Am Soc Nephrol* 2022; 33:1073–1075. doi: 10.1681/ASN.2021111515
7. Bletsa E, et al. Effect of dapagliflozin on urine metabolome in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2021; 106:1269–1283. doi: 10.1210/clinem/dgab086
8. Pak CY, et al. Spontaneous precipitation of brushite in urine: Evidence that brushite is the nidus of renal stones originating as calcium phosphate. *Proc Natl Acad Sci USA* 1971; 68:1456–1460. doi: 10.1073/pnas.68.7.1456
9. Maalouf NM, et al. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int* 2004; 65:1422–1425. doi: 10.1111/j.1523-1755.2004.00522.x
10. Onishi A, et al. A role for tubular Na^+/H^+ exchanger NHE3 in the natriuretic effect of the SGLT2 inhibitor empagliflozin. *Am J Physiol Renal Physiol* 2020; 319:F712–F728. doi: 10.1152/ajprenal.00264.2020
11. Wiederkehr MR, Moe OW. Uric acid nephrolithiasis: A systemic metabolic disorder. *Clin Rev Bone Miner Metab* 2011; 9:207–217. doi: 10.1007/s12018-011-9106-6

SGLT2i and nephrolithiasis risk in patients with type 2 diabetes

KidneyNews

Methods and Cohort

- Population-based, new-user cohort comparator study from the United States
- Adults with type 2 diabetes mellitus
- ❖ 1:1 Propensity matching
- ❖ Those initiated on SGLT2i
- ❖ Comparator drugs GLP-1RA, DPP4i
- Database from 3 sources: ➢Clinformatics ➢IBM MarketScan ➢Medicare
- Enrollment period: April 2013–December 2020
- Median follow-up period: 192 days

Primary Outcome: Nephrolithiasis in inpatient/outpatient

	No. of events (IR per 1000 PY)		RD per 1000 PY (95% CI)	HR (95% CI)
SGLT2i vs GLP-1RA N = 716,406	SGLT2i	GLP-1RA	-6.4 (-7.1 to 5.7)	0.69 (0.67 to 0.72)
	14.9	21.3		
SGLT2i vs DPP4i N = 662,056	SGLT2i	DPP4i	-5.3 (-6.0 to 4.6)	0.74 (0.71 to 0.77)
	14.6	19.9		

Conclusions: In adults with type 2 diabetes mellitus, SGLT2i may lower the risk of nephrolithiasis compared with GLP-1RA or DPP4i, which could help decision-making of glucose-lowering agents for patients who may be at risk for nephrolithiasis.

Paik JM, et al. **Sodium-glucose cotransporter 2 inhibitors and nephrolithiasis risk in patients with type 2 diabetes.** *JAMA Intern Med* 2024; 184:265–274. doi:10.1001/jamainternmed.2023.7660

CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person-years; RD, rate difference.

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