Journal of Health and Rehabilitation Research 2791-156X JHRR

For contributions to JHRR, contact at email: editor@jhrlmc.com

Systematic Review

SGLT-2 Inhibitors and Their Correlation with Kidney Stones. A Systematic Review

Bander J. Alshehri[1]*, Hani Sadaka Shalabi[2]

[1]Department of Medicine, College of Medicine, University of Jeddah, Jeddah, Saudi Arabia.

[2]Department of Internal Medicine, College of Medicine, University of Jeddah, Jeddah, Saudi Arabia.

Corresponding Author: Bander J. Alshehri; Email: Balshehri@uj.edu.sa

Conflict of Interest: None.

Alshehri BJ., et al. (2024). 4(2): DOI: https://doi.org/10.61919/jhrr.v4i2.743

ABSTRACT

Background: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have emerged as a valuable class of medications for managing Type 2 Diabetes Mellitus (T2DM) due to their efficacy in glycemic control and cardiovascular and renal benefits. However, concerns have been raised regarding their potential association with an increased risk of kidney stone formation.

Objective: This systematic review aimed to comprehensively evaluate the existing literature to determine the association between SGLT-2 inhibitors and kidney stone formation, elucidate potential underlying mechanisms, and discuss implications for clinical practice.

Methods: A systematic search of databases including PubMed, Google Scholar, Web of Sciences, Medline, and Scopus was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant research articles investigating the utilization of SGLT-2 inhibitors in humans and their potential correlation with kidney stones were included. Data extraction and quality assessment were performed, and a mixed-methods synthesis approach was used for data analysis.

Results: The systematic review identified several studies examining the association between SGLT-2 inhibitors and kidney stones. Overall, SGLT-2 inhibitors were found to be associated with a potential protective effect against kidney stone formation. Mechanistically, SGLT-2 inhibitors promote glycosuria and natriuresis, leading to increased urine flow rate and enhanced urinary volume, which may help dilute and flush out stone-forming substances. However, certain limitations and considerations, including potential adverse events and variations in study designs, were also highlighted.

Conclusion: This systematic review provides valuable insights into the potential correlation between SGLT-2 inhibitors and kidney stones. While the observed protective effect against kidney stone formation is promising, further research with longer follow-up durations and larger sample sizes is warranted to establish a more conclusive understanding of this relationship. Nonetheless, clinicians should remain vigilant in monitoring patients using SGLT-2 inhibitors and carefully assess individual risk factors when prescribing these medications.

Keywords: Sodium-glucose cotransporter-2 inhibitors, SGLT-2 inhibitors, kidney stones, Type 2 Diabetes Mellitus, glycemic control.

INTRODUCTION

Kidney stone disease, characterized by the formation of crystal concretions within the kidneys, is a significant urological disorder affecting approximately 12% of the global population and leading to considerable morbidity (1,2). The prevalence of kidney stones varies globally, ranging from 1-5% in Asia to 7-13% in the Americas, with Europe reporting rates between 5-9% (3). Given the high recurrence rates and associated morbidity of symptomatic stone disease, there is a clear and pressing need for effective medical prophylaxis (4). Despite all kidney stones presenting with similar symptoms (5), research has identified five primary mechanisms responsible for their formation: urinary supersaturation and crystallization, the influence of sex hormones, microbiome interactions, Randall's plaques, and immune responses (6). Risk factors for kidney stones include elevated serum calcium levels, increased total triglyceride and fasting insulin levels, and higher urine pH, along with genetically predicted urinary sodium, serum phosphorus levels, and tea consumption (7).

Over the past two decades, literature on the pathophysiology and treatment of kidney stones has seen no significant advancements, maintaining the challenge they pose to healthcare systems, physicians, and patients alike (8). Insulin resistance, a hallmark of type

2 diabetes mellitus (T2DM), may increase the likelihood of kidney stone formation, further exacerbated by chronic hyperglycemia (9,10). Additionally, individuals with kidney stones often suffer from a spectrum of comorbidities including obesity, hypertension, gout, cardiovascular diseases, dyslipidemia, low bone mass, and chronic renal diseases, all of which contribute significantly to the morbidity and mortality associated with stone-related disorders (11-15). While treatment options have matured, limitations persist in effectively reducing the incidence and recurrence of stones, necessitating the development of effective preventative and therapeutic strategies (16). Recommendations for managing kidney stone disease currently include increased fluid intake, dietary modifications to decrease the risk of calcium stones, and the use of medicinal plants, with several guidelines published to aid prevention efforts (17-20).

Amidst these conventional approaches, Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a potential preventative measure for nephrolithiasis by enhancing urine flow and offering additional benefits such as promoting weight loss, reducing blood pressure, and managing chronic kidney diseases, thereby increasing urinary volume and decreasing the concentration of lithogenic substances in urine (21-26). Despite these promising observations, clinical data supporting the impact of SGLT-2 inhibitors on preventing nephrolithiasis has been sparse, with one retrospective study using Danish health registries indicating a significant risk reduction of nearly 50% in incident nephrolithiasis among patients initiating SGLT-2 inhibitor therapy compared to those who began treatment with glucagon-like peptide-1 receptor agonists (21). However, concerns regarding the renal safety of these medications have prompted warnings from the US Food and Drug Administration (FDA), although no further regulatory action has been deemed necessary at this time (27).

This systematic review aims to explore the potential link between SGLT-2 inhibitors and kidney stone formation, marking a critical area of investigation in the context of the diabetes pandemic and its associated increase in kidney stone disease. Establishing a correlation, if any, between these inhibitors and kidney stone formation is essential not only for understanding the underlying mechanisms but also for developing strategies to mitigate this risk and ensure the safe and effective use of these medications. This study offers significant insights that could aid healthcare professionals and individuals in making informed decisions regarding the use of SGLT-2 inhibitors, ultimately enhancing patient care quality. To our knowledge, this is the first systematic review to specifically address the correlation between SGLT-2 inhibitors and kidney stones, underscoring its importance in current medical research and practice.

MATERIAL AND METHODS

This systematic review was carried out in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (28). A comprehensive literature search was conducted using databases including PubMed, Google Scholar, Web of Sciences, Medline, and Scopus to identify relevant research articles. The search strategy incorporated both MeSH terms and keywords such as "Sodium-glucose cotransporter-2 inhibitors," "Kidney stones," "SGLT-2is," and "Reno-protective," utilizing Boolean operators AND, OR, and NOT to refine the search results (Supplementary Table 1).

The inclusion criteria for the review specified that only primary research studies published in peer-reviewed journals were considered. Eligible studies involved human subjects and focused on the use of SGLT-2 inhibitors, particularly investigating their association with the occurrence or prevention of kidney stones. All selected studies were required to be published in English and encompass data from the inception of the respective databases to the present.

Conversely, exclusion criteria ruled out studies based on animal or in vitro models, as well as systematic reviews, meta-analyses, narrative reviews, commentaries, editorials, letters, conference abstracts, case studies, and book chapters. Publications not in English, studies not explicitly exploring the relationship between SGLT-2 inhibitors and kidney stones, and duplicates or overlapping studies were also excluded. Furthermore, the review did not consider grey literature such as unpublished studies, dissertations, and theses, or studies focusing on other medications or interventions not directly related to SGLT-2 inhibitors.

For study selection and assessment, titles and abstracts of articles retrieved were independently screened by two reviewers. Full-text articles that met the inclusion criteria were subsequently reviewed in detail, and any disagreements between reviewers were resolved through discussion or consultation with a third, impartial reviewer. Data extraction was conducted using a standardized form and included comprehensive details such as authors, country of research, study design, study population characteristics (diabetic or non-diabetic), sample size, demographics (gender, age, BMI), medical history (history of kidney stone, comorbidities, medication history), study duration, type and dose of SGLT-2 inhibitor, control conditions, associated diabetic drugs, other medications, primary outcomes related to kidney stones (incidence, prevalence, risk), secondary outcomes (stone composition, size, recurrence rates), adverse events, follow-up period, findings, conclusions, and study limitations.

The quality of the studies was assessed using the Mixed Methods Appraisal Tool (MMAT), and studies were categorized as low (scoring ≤3) or high quality (score >3) based on a point system where each positive answer to methodological quality questions scored 1 point (29,30). Data analysis integrated both qualitative and quantitative findings using a mixed-methods synthesis approach based on thematic analysis to ensure a comprehensive evaluation of the evidence (31). This rigorous methodology ensures that the findings of this systematic review are robust and provide a clear picture of the current understanding of the effects of SGLT-2 inhibitors on kidney stone risk.

RESULTS

In this systematic review, various studies evaluated the incidence and risk factors associated with nephrolithiasis among patients treated with Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors). The review included data from several types of research designs, including randomized controlled trials (RCTs), cohort studies, cross-sectional studies, and observational studies.

From the randomized controlled trial conducted by Haneda et al. (2016), the incidence of kidney stones in the placebo group was reported at 2%, though no actual cases were noted in the treated groups during the 28-week follow-up (Table 4). In contrast, Balasubramanian et al. (2022) reported a significantly lower incidence of urinary tract stones in patients treated with Empagliflozin, with an incidence rate ratio (IRR) of 0.64 (95% CI, 0.48-0.86), highlighting a 40% reduction in risk compared to the placebo group.

In the cohort study by Kristensen et al. (2021), a lower rate of nephrolithiasis was observed among patients initiating treatment with SGLT2 inhibitors compared to those initiating treatment with Glucagon-like Peptide-1 Receptor Agonists (GLP1 RA). The incidence was reported as 2.0 per 1000 person-years for the SGLT2 inhibitor group versus 4.0 for the GLP1 RA group, over an average follow-

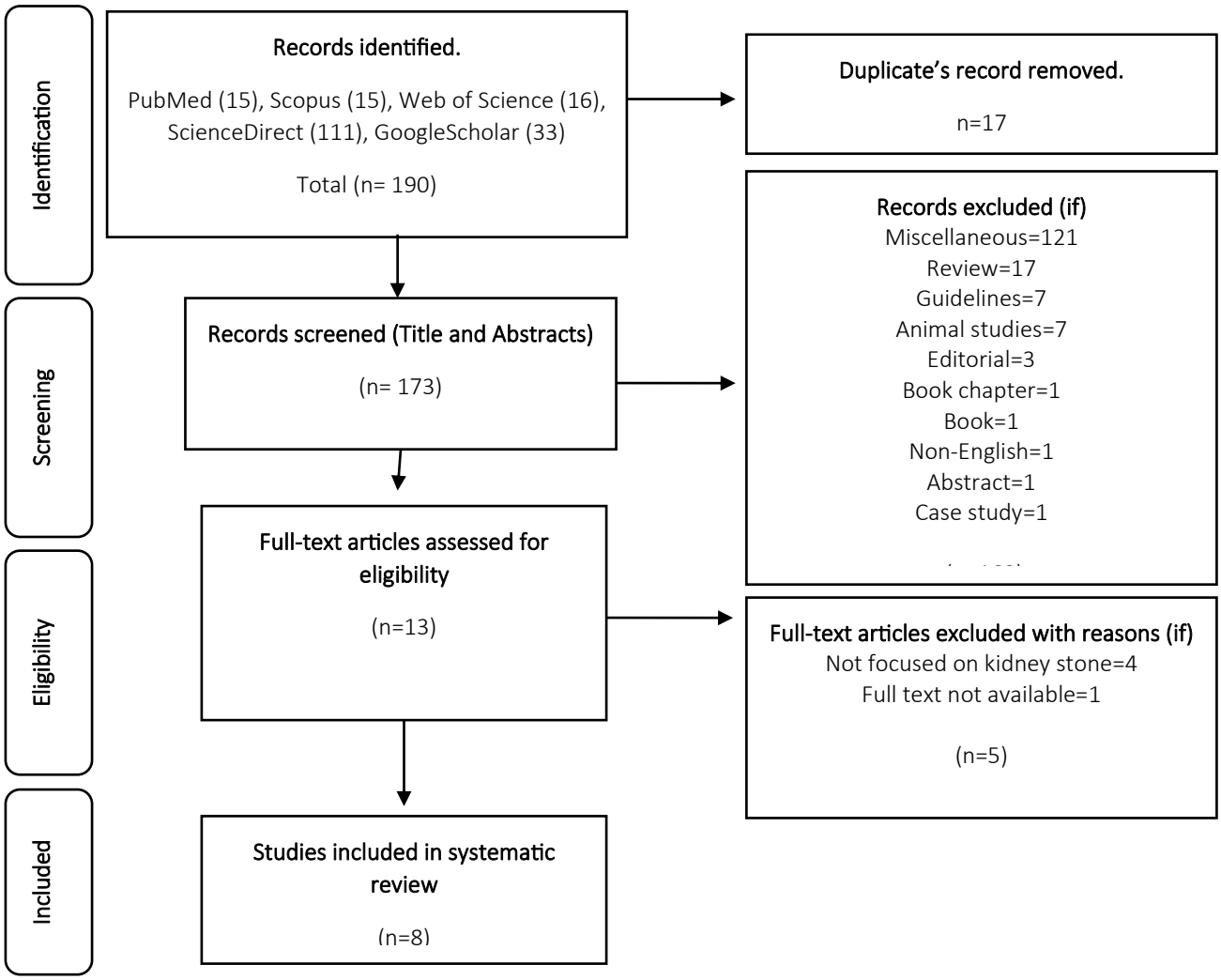

Figure 1 Systematic Review Selection Process

up of 2.1 years for the SGLT2 inhibitor group and 1.9 years for the GLP1 RA group. Varshney et al. (2021), another cohort study, observed no significant difference in genitourinary infection incidence within a 6-month period following the initiation of SGLT2 inhibitors compared to GLP1-RA.

In the cross-sectional study by Anan et al. (2022), a notable finding was the lower prevalence of nephrolithiasis in diabetic men treated with SGLT2 inhibitors compared to those not treated with these inhibitors. The SGLT2 inhibitor group showed a nephrolithiasis incidence of 2.28%, slightly lower than the 2.54% observed in the non-SGLT2 inhibitor group.

Table 1 Study Characteristics

Authors (Year)	Country	Design	Population	Sample Size	Gender M/F	Age	BMI	Kidney Stones
Davies et al. (2015)	USA	Post hoc	T2DM	C100mg: 833, C300mg: 834, P: 646	C100mg: 55.9, C300mg: 59.1, P: 56.3	C100mg: 32.3, C300mg: 32, P: 31.9	NA	
Haneda et al. (2016)	Japan	RCT	T2DM	145	111/34	68	NA	NA
Kristensen et al. (2021)	Denmark	Cohort	Diabetic/Non-diabetic	24650	SGLT2I: 6968, GLP1 RA: 7023	61	NA	NA
Varshney et al. (2021)	USA	Retrospective	T2DM	133	84/49	73.9	20-67	NA
Anan et al. (2022)	Japan	Cross-sectional	Diabetic	909,628	SGLT2 I: 158,070, Non-SGLT2 I: 1,380,128	20->80	NA	NA
Balasubramanian et al. (2022)	USA	RCT	T2DM	15081	I: 3623 F, P: 1761 F	60.6	I: 30.47, P: 30.36	I: 3, P: 6
Frent et al. (2022)	Romania	Observational	T2DM	231	114/90	18->75	NA	NA
Harmacek et al. (2022)	Switzerland	Post hoc	Healthy	45	27/18	33.4	28.2	None

Table 2 Study Characteristics related to Outcome

Authors (Year)	Comorbidities	Incidence	Duration	SGLT2 Inhibitor & Dose	Diabetic Drugs	Other Drugs	Recurrence	Adverse Events
Davies et al. (2015)	NA	Placebo: 0.2%	NA	Canagliflozin (100-300mg)	NA	NA	NA	NA
Haneda et al. (2016)	NA	Placebo: 2%	NA	Luseogliflozin (2.5-5mg/d)	NA	NA	NA	Mild AEs
Kristensen et al. (2021)	Multiple comorbidities	SGLT2 I: 58, GLP1 RA: 108	NA	SGLT2 Is	Multiple drugs	Multiple drugs	SGLT2 I: 54, GLP1 RA: 74	NA
Varshney et al. (2021)	Multiple urinary issues	8.30%	NA	Empagliflozin, Canagliflozin, Dapagliflozin	NA	NA	NA	NA
Anan et al. (2022)	NA	SGLT2 I: 2.28%, Non-SGLT2 I: 2.54%	NA	SGLT2 Is	NA	NA	NA	NA

Authors (Year)	Comorbidities	Incidence	Duration	SGLT2 Inhibitor & Dose	Diabetic Drugs	Other Drugs	Recurrence	Adverse Events
Balasubramanian et al. (2022)	Hypertension, lithiasis	Intervention: 75, Placebo: 57	549/543	Empagliflozin (25mg)	Insulin, Sulfonylurea	Anti-gout meds	1 patient	Various urological
Frent et al. (2022)	NA	NA	NA	Gliflozins	NA	NA	0	Severe AEs
Harmacek et al. (2022)	None	NA	None	Empagliflozin (10mg)	None	None	NA	NA

Table 3 Study Characteristics regarding Findings and Conclusions

Authors (Year)	Follow-up	Key Findings	Conclusions	Limitations
Davies et al. (2015)	NA	Hyperuricemic patients on canagliflozin had significant uric acid level reductions.	Canagliflozin lowers serum uric acid in T2DM, potentially reducing gout and kidney stones.	NA
Haneda et al. (2016)	28 weeks	Luseogliflozin lowered HbA1c, FPG, and body weight; minimal AEs.	Luseogliflozin is effective and well-tolerated in Japanese T2DM patients with renal impairment.	Small sample size
Kristensen et al. (2021)	SGLT2I: 2.1 years, GLP1 RA: 1.9 years	Lower nephrolithiasis rates in patients with SGLT2 inhibitors compared to GLP1 RA.	SGLT2 inhibitors may decrease first and recurrent nephrolithiasis.	NA
Varshney et al. (2021)	6 months	No difference in GUI incidence between SGLT2i and GLP1-RA.	No increased UTI risk with SGLT2Is.	Small sample, Study design, No adherence check.
Anan et al. (2022)	NA	Diabetic men on SGLT2 inhibitors had lower nephrolithiasis prevalence.	SGLT2 inhibitors could help prevent renal stones.	Duration of SGLT2i use not specified.
Balasubramanian et al. (2022)	Unclear	Empagliflozin showed a positive impact on reducing urinary tract stone risk (IRR: 0.64).	Empagliflozin may reduce stone risk in T2DM by 40%.	Missing data, Post hoc analysis
Frent et al. (2022)	NA	Canagliflozin associated with higher nephrolithiasis cases.	Gliflozins linked to increased nephrolithiasis incidents.	NA
Harmacek et al. (2022)	NA	SGLT2 inhibitors decreased CaP saturation without RSR change.	SGLT2 inhibitors might lower the risk of calcium-based kidney stones in healthy individuals.	NA

Table 4 Quality Assessment

Study Id	Design	MMAT Criteria	Score
Haneda et al. (2016)	RCT	2.1: Y, 2.2: Y, 2.3: Y, 2.4: CT, 2.5: Y	4
Balasubramanian et al. (2022)	RCT	2.1: Y, 2.2: Y, 2.3: Y, 2.4: CT, 2.5: Y	4
Kristensen et al. (2021)	Cohort	3.1: Y, 3.2: Y, 3.3: Y, 3.4: Y, 3.5: Y	5
Varshney et al. (2021)	Cohort	3.1: Y, 3.2: Y, 3.3: Y, 3.4: Y, 3.5: Y	5
Anan et al. (2022)	Cross-sectional	4.1: Y, 4.2: Y, 4.3: Y, 4.4: CT, 4.5: Y	4

Journal of Health and Rehabilitation Research 2791-156X JHRR

Frent et al. (2022)	Observational	4.1: Y, 4.2: Y, 4.3: Y, 4.4: CT, 4.5: Y	4
Davies et al. (2015)	Post hoc	5.1: Y, 5.2: Y, 5.3: Y, 5.4: Y, 5.5: Y	5
Harmacek et al. (2022)	Post hoc	5.1: Y, 5.2: Y, 5.3: Y, 5.4: Y, 5.5: Y	5

Additionally, Davies et al. (2015) in their post hoc analysis found that despite the subgroup of hyperuricemic patients experiencing a significant reduction in serum uric acid levels, the occurrences of kidney stones were relatively low and similar across different treatment groups, including the placebo. Lastly, the observational study by Frent et al. (2022) found that Canagliflozin was the gliflozin most frequently associated with cases of nephrolithiasis, representing 109 out of 231 cases observed, highlighting a potentially higher incidence of nephrolithiasis with this specific inhibitor.

Each study was rigorously assessed for methodological quality using the Mixed Methods Appraisal Tool (MMAT), with scores ranging from 4 to 5, indicating a generally high quality of the included studies (Table 4). These findings provide robust evidence regarding the effects of SGLT2 inhibitors on kidney stone formation and recurrence, contributing significantly to the understanding of their renal safety profile and therapeutic potential in patients with Type 2 Diabetes Mellitus.

DISCUSSION

The association between Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and kidney stone formation has garnered significant attention in the medical community due to the expanding use of these medications in managing Type 2 Diabetes Mellitus (T2DM). SGLT-2 inhibitors have demonstrated substantial efficacy in glycemic control and have been associated with cardiovascular and renal benefits in individuals with T2DM (39, 40). However, concerns have arisen regarding their potential link to an increased risk of kidney stone formation when compared to other antihyperglycemic medications (37). In light of these concerns, a systematic review was conducted to comprehensively evaluate the existing literature regarding the association between SGLT-2 inhibitors and kidney stones. The discussion aims to synthesize the findings, elucidate potential underlying mechanisms, and discuss the implications for clinical practice.

The systematic review revealed a notable trend suggesting a potential protective effect of SGLT-2 inhibitors against kidney stone formation. This observation aligns with the pharmacological mechanism of SGLT-2 inhibitors, which selectively inhibit the SGLT-2 protein in the proximal tubules of the kidneys, thereby promoting glycosuria and natriuresis (41). By increasing glucose and sodium excretion in the urine, SGLT-2 inhibitors induce a diuretic effect, leading to enhanced urine flow rate and increased urinary volume. This diuretic effect aids in diluting and flushing out stone-forming substances, consequently reducing the risk of kidney stone formation (42, 43). Furthermore, SGLT-2 inhibitors have been associated with decreased uric acid levels in the urine, thereby further contributing to the prevention of stone formation (44).

The observed protective effect of SGLT-2 inhibitors against kidney stone formation is reinforced by their potential to improve insulin sensitivity and reduce hyperinsulinemia (45, 46). Insulin resistance and hyperinsulinemia have been implicated in stone development, suggesting that the beneficial metabolic effects of SGLT-2 inhibitors may indirectly reduce the risk of kidney stone formation.

However, despite the overall favorable outcomes associated with SGLT-2 inhibitors, the systematic review also highlighted certain limitations and considerations. Recurrence of stone formation, albeit of mild nature, was observed in some cases following the use of SGLT-2 inhibitors. Additionally, while the observed protective effect against kidney stone formation is promising, it is essential to acknowledge that not all individuals taking these medications will experience this benefit (4). Moreover, like all medications, SGLT-2 inhibitors are associated with potential adverse events (AEs). Common AEs include an increased risk of urinary tract infections (UTIs) due to increased glucose excretion in the urine, as well as genital yeast infections, increased urination, and potential hypotension (51).

Furthermore, the review's strengths lie in its comprehensive and methodical analysis of the existing literature, ensuring a thorough examination of all relevant studies. The transparent reporting of methodology and results enhances the reproducibility and validation of findings by other researchers. However, the review's limitations include potential biases or methodological variations in the included studies, as well as the absence of data from certain populations or regions, limiting the generalizability of conclusions. Additionally, the relatively short follow-up durations in some studies pose challenges in assessing the long-term impact of SGLT-2 inhibitors on kidney stone formation.

CONCLUSION

In conclusion, this systematic review provides valuable insights into the potential correlation between SGLT-2 inhibitors and kidney stones. While the observed protective effect against kidney stone formation is promising, further research with longer follow-up

durations and larger sample sizes is warranted to establish a more conclusive understanding of this relationship. Nonetheless, clinicians should remain vigilant in monitoring patients using SGLT-2 inhibitors and carefully assess individual risk factors when prescribing these medications. Overall, this review underscores the importance of continued research and surveillance to optimize the safe and effective use of SGLT-2 inhibitors in clinical practice.

REFERENCES

1. Alelign T, Petros B. Kidney Stone Disease: An Update on Current Concepts. Adv Urol. 2018;2018:3068365.
2. Moftakhar L, Jafari F, Ghoddusi Johari M, Rezaeianzadeh R, Hosseini SV, Rezaianzadeh A. Prevalence and risk factors of kidney stone disease in population aged 40–70 years old in Kharameh cohort study: a cross-sectional population-based study in southern Iran. BMC Urol. 2022;22(1):205.
3. Sorokin I, Mamoulakis C, Miyazawa K, Rodgers A, Talati J, Lotan Y. Epidemiology of stone disease across the world. World J Urol. 2017;35(9):1301-20.
4. Schietzel S, Bally L, Cereghetti G, Faller N, Moor MB, Vogt B, et al. Impact of the SGLT2 inhibitor empagliflozin on urinary supersaturations in kidney stone formers (SWEETSTONE trial): protocol for a randomised, double-blind, placebo-controlled cross-over trial. BMJ Open. 2022;12(3):e059073.
5. Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. Pediatr Nephrol. 2010;25(5):831-41.
6. Wang Z, Zhang Y, Zhang J, Deng Q, Liang H. Recent advances on the mechanisms of kidney stone formation (Review). Int J Mol Med. 2021;48(2):149.
7. Liu W, Wang M, Liu J, Yan Q, Liu M. Causal effects of modifiable risk factors on kidney stones: a bidirectional mendelian randomization study. BMC Med Genomics. 2023;16(1):82.
8. Stamatelou K, Goldfarb DS. Epidemiology of Kidney Stones. Healtcare. 2023;11(3):424.
9. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int. 2005;68(3):1230-5.
10. Geraghty R, Abdi A, Somani B, Cook P, Roderick P. Does chronic hyperglycaemia increase the risk of kidney stone disease? results from a systematic review and meta-analysis. BMJ Open. 2020;10(1):e032094.
11. Madore F, Stampfer MJ, Willett WC, Speizer FE, Curhan GC. Nephrolithiasis and risk of hypertension in women. Am J Kidney Dis. 1998;32(5):802-7.
12. Taylor EN, Curhan GC. Body size and 24-hour urine composition. Am J Kidney Dis. 2006;48(6):905-15.
13. Liu Y, Li S, Zeng Z, Wang J, Xie L, Li T, et al. Kidney stones and cardiovascular risk: a meta-analysis of cohort studies. Am J Kidney Dis. 2014;64(3):402-10.
14. Alexander RT, Hemmelgarn BR, Wiebe N, Bello A, Morgan C, Samuel S, et al. Kidney stones and kidney function loss: a cohort study. BMJ. 2012;345.
15. Sakhaee K, Maalouf NM, Kumar R, Pasch A, Moe OW. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. Kidney Int. 2011;79(4):393-403.
16. Chen T, Qian B, Zou J, Luo P, Zou J, Li W, et al. Oxalate as a potent promoter of kidney stone formation. Frontr Med. 2023;10.
17. Deepak R, Mukesh K. Role of herbal medicines in the treatment of Kidney stone: A brief review. Adv Pharmaceut J 2022;7(5):149-54.
18. Zisman AL. Effectiveness of Treatment Modalities on Kidney Stone Recurrence. Clin J Am Soc Nephrol. 2017;12(10):1699-708.
19. Phien HH, Men TT. Overview of Kidney Stones and the Potential of Natural Compounds for the Treatment. Res Highlights Dis Health Res. 2023;1:11-23.
20. Pearle M, Goldfarb D, Assimos D. Medical management of kidney stones: AUA Guideline. J Urol. 2014;192:316.
21. Kristensen KB, Henriksen DP, Hallas J, Pottegård A, Lund LC. Sodium-glucose cotransporter 2 inhibitors and risk of nephrolithiasis. Diabetologia. 2021;64(7):1563-71.
22. Refardt J, Winzeler B, Meienberg F, Vogt DR, Christ-Crain M. Empagliflozin Increases Short-Term Urinary Volume Output in Artificially Induced Syndrome of Inappropriate Antidiuresis. Int J Endocrinol. 2017;2017:7815690.
23. Seman L, Macha S, Nehmiz G, Simons G, Ren B, Pinnetti S, et al. Empagliflozin (BI 10773), a Potent and Selective SGLT2 Inhibitor, Induces Dose-Dependent Glucosuria in Healthy Subjects. CPDD. 2013;2(2):152-61.

24. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetol. 2018;61(12):2461-98.
25. Cheungpasitporn W, Rossetti S, Friend K, Erickson SB, Lieske JC. Treatment effect, adherence, and safety of high fluid intake for the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. J Nephrol. 2016;29(2):211-9.
26. van Bommel EJM, Muskiet MHA, Tonneijck L, Kramer MHH, Nieuwdorp M, van Raalte DH. SGLT2 Inhibition in the Diabetic Kidney—From Mechanisms to Clinical Outcome. Clin J Am Soc Nephrol. 2017;12(4):700-10.
27. FDA U. Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) US: FDA; 2017 [Available from: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/january-march-2017-potential-signals-serious-risksnew-safety-information-identified-fda-adverse.
28. Page MJ, Moher D, McKenzie JE. Introduction to PRISMA 2020 and implications for research synthesis methodologists. Research Synthesis Methods. 2022;13(2):156-63.
29. Charette M, McKenna LG, Deschênes M-F, Ha L, Merisier S, Lavoie P. New graduate nurses' clinical competence: A mixed methods systematic review. Journal of Advance Nursing. 2020;76(11):2810-29.
30. Hong QN, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. Education for information. 2018;34(4):285-91.
31. Noyes J, Booth A, Moore G, Flemming K, Tunçalp Ö, Shakibazadeh E. Synthesising quantitative and qualitative evidence to inform guidelines on complex interventions: clarifying the purposes, designs and outlining some methods. BMJ Global Health 2019;4(Suppl 1):e000893.
32. Davies MJ, Trujillo A, Vijapurkar U, Damaraju CV, Meininger G. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2015;17(4):426-9.
33. Varshney N, Billups SJ, Saseen JJ, Fixen CW. Sodium-glucose cotransporter-2 inhibitors and risk for genitourinary infections in older adults with type 2 diabetes. Ther Adv Drug Saf. 2021;12:2042098621997703.
34. Balasubramanian P, Wanner C, Ferreira JP, Ofstad AP, Elsaesser A, Zinman B, et al. Empagliflozin and Decreased Risk of Nephrolithiasis: A Potential New Role for SGLT2 Inhibition? J Clin Endocrinol Metab. 2022;107(7):e3003-e7.
35. Haneda M, Seino Y, Inagaki N, Kaku K, Sasaki T, Fukatsu A, et al. Influence of Renal Function on the 52-Week Efficacy and Safety of the Sodium Glucose Cotransporter 2 Inhibitor Luseogliflozin in Japanese Patients with Type 2 Diabetes Mellitus. Clin Ther. 2016;38(1):66-88.e20.
36. Anan G, Hirose T, Kikuchi D, Takahashi C, Endo A, Ito H, et al. Inhibition of sodium-glucose cotransporter 2 suppresses renal stone formation. Pharmacol Res. 2022;186:106524.
37. Frent I, Leucuta D, Bucsa C, Farcas A, Casoinic F, Mogosan C. A Description of Acute Renal Failure and Nephrolithiasis Associated With Sodium-Glucose Co-Transporter 2 Inhibitor Use: A VigiBase Study. Front Pharmacol. 2022;13:925805.
38. Harmacek D, Pruijm M, Burnier M, Muller ME, Ghajarzadeh-Wurzner A, Bonny O, et al. Empagliflozin Changes Urine Supersaturation by Decreasing pH and Increasing Citrate. J Am Soc Nephrol. 2022;33(6):1073-5.
39. Baruah MP, Makkar BM, Ghatnatti VB, Mandal K. Sodium Glucose Co-transporter-2 Inhibitor: Benefits beyond Glycemic Control. Indian J Endocrinol Metab. 2019;23(1):140-9.
40. Rabizadeh S, Nakhjavani M, Esteghamati A. Cardiovascular and Renal Benefits of SGLT2 Inhibitors: A Narrative Review. Int J Endocrinol Metab. 2019;17(2):e84353.
41. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017;24(1):73-9.
42. Aggarwal A, Jain A, Sachdeva S, Kulairi ZI. Prolonged Glucosuria With Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A Case Report and Review of Literature. Cureus. 2020;12(11):e11554.
43. Ansary TM, Nakano D, Nishiyama A. Diuretic Effects of Sodium Glucose Cotransporter 2 Inhibitors and Their Influence on the Renin-Angiotensin System. Int J Mol Sci. 2019;20(3).
44. Thomas MC. Renal effects of dapagliflozin in patients with type 2 diabetes. Ther Adv Endocrinol Metab. 2014;5(3):53-61.
45. Hosokawa Y, Ogawa W. SGLT2 inhibitors for genetic and acquired insulin resistance: Considerations for clinical use. J Diabetes Investig. 2020;11(6):1431-3.
46. Janssen JAMJL. Hyperinsulinemia and Its Pivotal Role in Aging, Obesity, Type 2 Diabetes, Cardiovascular Disease and Cancer. Int J Mol Sci 2021;22(15):7797.
47. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. Ann Rev Physiol. 2021;83(1):503-28.

Journal of Health and Rehabilitation Research 2791-156X JHRR

48. Sarafidis PA, Ortiz A. The risk for urinary tract infections with sodium-glucose cotransporter 2 inhibitors: no longer a cause of concern? Clin Kidney J. 2020;13(1):24-6.

49. Unnikrishnan AG, Kalra S, Purandare V, Vasnawala H. Genital Infections with Sodium Glucose Cotransporter-2 Inhibitors: Occurrence and Management in Patients with Type 2 Diabetes Mellitus. Indian J Endocrinol Metab. 2018;22(6):837-42.

50. John M, Gopinath D, Jagesh R. Sodium-glucose cotransporter 2 inhibitors with insulin in type 2 diabetes: Clinical perspectives. Indian J Endocrinol Metab. 2016;20(1):22-31.

51. Keller DM, Ahmed N, Tariq H, Walgamage M, Walgamage T, Mohammed A, et al. SGLT2 Inhibitors in Type 2 Diabetes Mellitus and Heart Failure-A Concise Review. J Clin Med. 2022;11(6).

52. Nadkarni GN, Ferrandino R, Chang A, Surapaneni A, Chauhan K, Poojary P, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. Diabetes Care. 2017;40(11):1479-85.