Systematic Review

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

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Conflict of Interest: None.

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 the 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-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.

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

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

Table 2 Study Characteristics related to Outcome

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Comorbiditie s</th>
<th>Incidence</th>
<th>Duratio n</th>
<th>SGLT2 Inhibitor &amp; Dose</th>
<th>Diabetic Drugs</th>
<th>Other Drugs</th>
<th>Recurrenc e</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al. (2015)</td>
<td>NA</td>
<td>Placebo: 0.2%</td>
<td>NA</td>
<td>Canagliflozin (100-300mg)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Haneda et al. (2016)</td>
<td>NA</td>
<td>Placebo: 2%</td>
<td>NA</td>
<td>Luseogliflozin (2.5-5mg/d)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Mild AEs</td>
</tr>
<tr>
<td>Kristensen et al. (2021)</td>
<td>Multiple comorbidities</td>
<td>SGLT2 I: 58, GLP1 RA: 108</td>
<td>NA</td>
<td>SGLT2 Is</td>
<td>Multiple drugs</td>
<td>Multipl e drugs</td>
<td>SGLT2 I: 54, GLP1 RA: 74</td>
<td>NA</td>
</tr>
<tr>
<td>Varshney et al. (2021)</td>
<td>Multiple urinary issues</td>
<td>8.30%</td>
<td>NA</td>
<td>Empagliflozin, Canagliflozin, Dapagliflozin</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Anan et al. (2022)</td>
<td>NA</td>
<td>SGLT2 I: 2.28%, Non-SGLT2 I: 2.54%</td>
<td>NA</td>
<td>SGLT2 Is</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>
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Table 3: Study Characteristics regarding Findings and Conclusions

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Follow-up</th>
<th>Key Findings</th>
<th>Conclusions</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al. (2015)</td>
<td>NA</td>
<td>Hyperuricemic patients on canagliflozin had significant uric acid level reductions.</td>
<td>Canagliflozin lowers serum uric acid in T2DM, potentially reducing gout and kidney stones.</td>
<td>NA</td>
</tr>
<tr>
<td>Haneda et al. (2016)</td>
<td>28 weeks</td>
<td>Luseogliflozin lowered HbA1c, FPG, and body weight; minimal AEs.</td>
<td>Luseogliflozin is effective and well-tolerated in Japanese T2DM patients with renal impairment.</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Kristensen et al. (2021)</td>
<td>SGLT2I: 2.1 years, GLP1 RA: 1.9 years</td>
<td>Lower nephrolithiasis rates in patients with SGLT2 inhibitors compared to GLP1 RA.</td>
<td>SGLT2 inhibitors may decrease first and recurrent nephrolithiasis.</td>
<td>NA</td>
</tr>
<tr>
<td>Varshney et al. (2021)</td>
<td>6 months</td>
<td>No difference in GUI incidence between SGLT2i and GLP1-RA.</td>
<td>No increased UTI risk with SGLT2is.</td>
<td>Small sample, Study design, No adherence check.</td>
</tr>
<tr>
<td>Anan et al. (2022)</td>
<td>NA</td>
<td>Diabetic men on SGLT2 inhibitors had lower nephrolithiasis prevalence.</td>
<td>SGLT2 inhibitors could help prevent renal stones.</td>
<td>Duration of SGLT2i use not specified.</td>
</tr>
<tr>
<td>Balasubramanian et al. (2022)</td>
<td>Unclear</td>
<td>Empagliflozin showed a positive impact on reducing urinary tract stone risk (IRR: 0.64).</td>
<td>Empagliflozin may reduce stone risk in T2DM by 40%.</td>
<td>Missing data, Post hoc analysis</td>
</tr>
<tr>
<td>Frent et al. (2022)</td>
<td>NA</td>
<td>Canagliflozin associated with higher nephrolithiasis cases.</td>
<td>Gliflozins linked to increased nephrolithiasis incidents.</td>
<td>NA</td>
</tr>
<tr>
<td>Harmacek et al. (2022)</td>
<td>NA</td>
<td>SGLT2 inhibitors decreased CaP saturation without RSR change.</td>
<td>SGLT2 inhibitors might lower the risk of calcium-based kidney stones in healthy individuals.</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 4: Quality Assessment

<table>
<thead>
<tr>
<th>Study Id</th>
<th>Design</th>
<th>MMAT Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haneda et al. (2016)</td>
<td>RCT</td>
<td>2.1: Y, 2.2: Y, 2.3: Y, 2.4: CT, 2.5: Y</td>
<td>4</td>
</tr>
<tr>
<td>Balasubramanian et al. (2022)</td>
<td>RCT</td>
<td>2.1: Y, 2.2: Y, 2.3: Y, 2.4: CT, 2.5: Y</td>
<td>4</td>
</tr>
</tbody>
</table>
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**TABLE 4**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Study Duration</th>
<th>Observational Hours</th>
<th>Potential Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frent et al. (2022)</td>
<td>Observational</td>
<td>4.1: Y, 4.2: Y, 4.3: Y, 4.4: CT, 4.5: Y</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

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


