The effect of SGLT2 inhibitors on kidney stones; a systematic review and meta-analysis

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Sodium-glucose cotransporter-2 (SGLT2) inhibitors are among the antidiabetic drugs with unclear relationship effect on kidney stones. Accordingly, this study aimed to investigate the relationship between SGLT2 inhibitors treatment and kidney calculi incidence using systematic review and meta-analysis.

Materials and Methods: The PRISMA statement was used to write this systematic review and meta-analysis. Databases, including ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar, were used to access the resources without a lower time limit until November 5, 2023. Data analysis was conducted using STATA 14 software.

Results: Results obtained from six studies with a total of 4963542 participants indicated that SGLT2 inhibitors administration reduced the possibility of kidney calculi in general (OR = 0.80, 95% CI: 0.72, 0.89), in men (OR = 0.92, 95% CI: 0.86, 0.98), and women (OR = 0.93, 95% CI: 0.89, 0.97). SGLT2 inhibitors treatment prevented kidney calculi in cross-sectional studies (OR = 0.92, 95% CI: 0.89, 0.96), cohort studies (OR = 0.71, 95% CI: 0.66, 0.77), RCT study (OR = 0.64, 95% CI: 0.48, 0.86), Japan (OR = 0.92, 95% CI: 0.89, 0.96), United States (OR = 0.72, 95% CI: 0.67, 0.76), Denmark (OR = 0.51, 95% CI: 0.37, 0.71), compared with DPP4i (OR = 0.74, 95% CI: 0.71, 0.77), compared with GLP1RA (OR = 0.62, 95% CI: 0.47, 0.82), compared with other antidiabetic drugs (OR = 0.92, 95% CI: 0.89, 0.96), and compared with placebo (OR = 0.64, 95% CI: 0.48, 0.86).

Conclusion: Compared with placebo and other antidiabetic drugs, SGLT2 inhibitors reduce the risk of kidney calculi. However, considering the limited number of investigated studies, more studies in this field are required.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023483132) and Research Registry (UIN: reviewregistry1743) websites.

Implication for health policy/practice/research/medical education:
In a meta-analysis study, we found that SGLT2 inhibitors have shown promise in reducing the risk of kidney calculi compared to placebo and other antidiabetic drugs. However, the number of studies investigating this effect is limited, and more research is needed in this field. Nonetheless, the potential benefits of SGLT2 inhibitors in reducing the risk of kidney stones make them a promising therapeutic approach against nephrolithiasis.

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Meta-analysis

Introduction

Kidney stone is among the most common diseases and costliest urology complications in the world, with a frequency of 10% and 6% in men and women, respectively (1). The recurrence possibility of kidney stones within five years is between 30% and 40%, and the possibility of recurrence within ten years is approximately 50% (2). Kidney stone is a multifactor disease, and factors including age, sex, geography, weather, race, diet, and genetic factors play roles in kidney stone incidence (3). Approximately 1 in every 11 individuals experience kidney stones during their lives, which can cause kidney obstruction and hydronephrosis and eventually lead to chronic kidney disease (CKD) (4). Generally, the risk of CKD or end-stage renal disease (ESRD) in patients with kidney calculi is more than twice the rate in normal individuals (5). On the other hand, most kidney stones are composed of calcium oxalate (CaOx) (6), and so far, there is no effective preventive drug or treatment for calcium oxalate stones (7,8). Accordingly, it would be best to identify the drugs that indirectly reduce the possibility of kidney stones.

Sodium-glucose cotransporter-2 (SGLT2) transporters are located on the border membrane of renal proximal tubular cells and reabsorb approximately 90% of the filtered glucose in the glomerulus (9). Besides controlling the blood glucose level, SGLT2 inhibitors (SGLT2i) also can reduce body weight and visceral fat, lower blood pressure, improve cardiovascular condition, and cause anti-inflammatory effects (1,6). Moreover, SGLT2i causes osmotic diuresis, polyuria, and isosthenuria, which can reduce the risk of kidney calculi (10). In theory, SGLT2 inhibitors may prevent kidney calculi by reducing the lithogenic substance's concentration in urine (11) and the circulating level of uric acid (12). However, another source reported nephrolithiasis among the possible side effects of the SGLT2i drug, and the Food and Drug Administration (FDA) has also issued a related warning (13). Since diabetes mellitus is associated with an increased risk of nephrolithiasis (14), and SGLT2 inhibitors are among the antidiabetic drugs, our goal was to investigate the relationship between the SGLT2 inhibitors treatment and kidney stones incidence by conducting a systematic review and meta-analysis.

Materials and Methods

Study design

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (15) was conducted to write the current systematic review and meta-analysis, and the protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) website.

Search strategy

Databases, including ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar Search Engine, were used to search without a lower time limit until November 5, 2023. Medical Subject Headings (MeSH) keywords and their equals "Kidney Calculi, Nephrolithiasis, Kidney Stone, Sodium-Glucose Transporter 2 Inhibitors, SGLT-2 Inhibitors, Gliflozins" were conducted to search for the sources. Then, the keywords were combined using the (AND, OR) operators, and the advanced search was conducted. The manual search also included a list of eligible study sources. Search study on the Web of Science website: Kidney Calculi OR Nephroliths OR Kidney Stone (All Fields) and Sodium-Glucose Transporter 2 Inhibitors OR SGLT-2 Inhibitors OR Gliflozine (All Fields).

PICO component

- Population: Studies that investigated the effect of SGLT2 inhibitors on kidney calculi;
- Intervention: SGLT2 inhibitors treatment
- Comparison: administration of other antidiabetic drugs or placebos
- Outcomes: incidence of kidney stones.

Inclusion and exclusion criteria

Studies that investigated the effect of SGLT2 inhibitors on kidney stones entered our study. On the other hand, duplicate studies, those with incomplete datasets, review articles, low-quality studies, descriptive studies, and protocols were excluded from our inquiry list.

Quality assessment

Cochrane institute's checklist was used to evaluate the RCT studies (16). The checklist includes seven questions, and each has three answers: a) high risk of bias, b) low risk of bias, and c) bias risk unknown. Each question evaluates one of the critical bias types in clinical trials. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to assess the observational studies (17). This checklist includes 22 questions. However, note that the minimum and maximum scores are 0 and 44, respectively. Then, two researchers evaluated the cases of disagreement regarding the answers to the questions and reached the same answer by consulting with each other.

Data extraction

Two researchers independently extracted the data from the investigated studies. The designed checklist for data extraction included the first author's name, type of the study, sample size, comparison group, study duration, age, location, and the odds ratio between the use of SGLT2 inhibitors and kidney calculi with its 95% confidence interval. The third researcher examined the extracted data of the two previous researchers and solved the inconsistencies.

Statistical analysis

The studies were combined using the OR logarithms,

and the I^2 index was used for heterogeneity assessment. The I^2 index included three subclasses (lower than 25%: low heterogeneity; between 25% and 75%: moderate heterogeneity; and higher than 75%: high heterogeneity) (18). The fixed effects and randomized effects models were used for low and high heterogeneities, respectively. Due to the high heterogeneity of the studies included in this study, we used the randomized effects model (I^2 = 96.5%). Data analysis was conducted using the STATA 14 software, and tests with P values lower than 0.05 ($P < 0.05$) were considered statistically significant.

Results

A total of 376 studies were searched using the mentioned databases. The study titles were reviewed, and 155 duplicate studies were removed. The abstracts of the remaining studies were investigated, and 49 studies without available full-text and those with incomplete abstracts were excluded. Out of the 172 remaining studies, 47 were removed as the required data for analysis was incomplete. In the next stage, the researchers reviewed 125 studies, and 119 were excluded due to other exclusion criteria. Eventually, six studies entered the systematic review and meta-analysis (Figure 1).

Table 1 presents a portion of the extracted data from the eligible studies.

Primary outcome

SGLT2 inhibitors administration reduced the risk of kidney calculi by 20% and prevented kidney stone disease (OR = 0.80, 95% CI: 0.72, 0.89) (Figure 2). SGLT2 inhibitors treatment in men (OR = 0.92, 95% CI: 0.86, 0.98) and women (OR = 0.93, 95% CI: 0.89, 0.97) also reduced the risk of kidney stone disease by 8% and 7%, respectively. However, note that only two of the six reviewed studies had provided the results of the male and female patients separately.

Analysis of subgroups

SGLT2 inhibitors treatment reduced the risk of kidney stone disease in cross-sectional (OR = 0.92, 95% CI: 0.89, 0.96), cohort (OR = 0.71, 95% CI: 0.66, 0.77), and RCT studies (OR = 0.64, 95% CI: 0.48, 0.86) (Figure 3).

SGLT2 inhibitors treatment reduced the risk of kidney calculi compared with the DPP4i (OR = 0.74, 95% CI: 0.71, 0.77), GLP1RA (OR = 0.62, 95% CI: 0.47, 0.82),
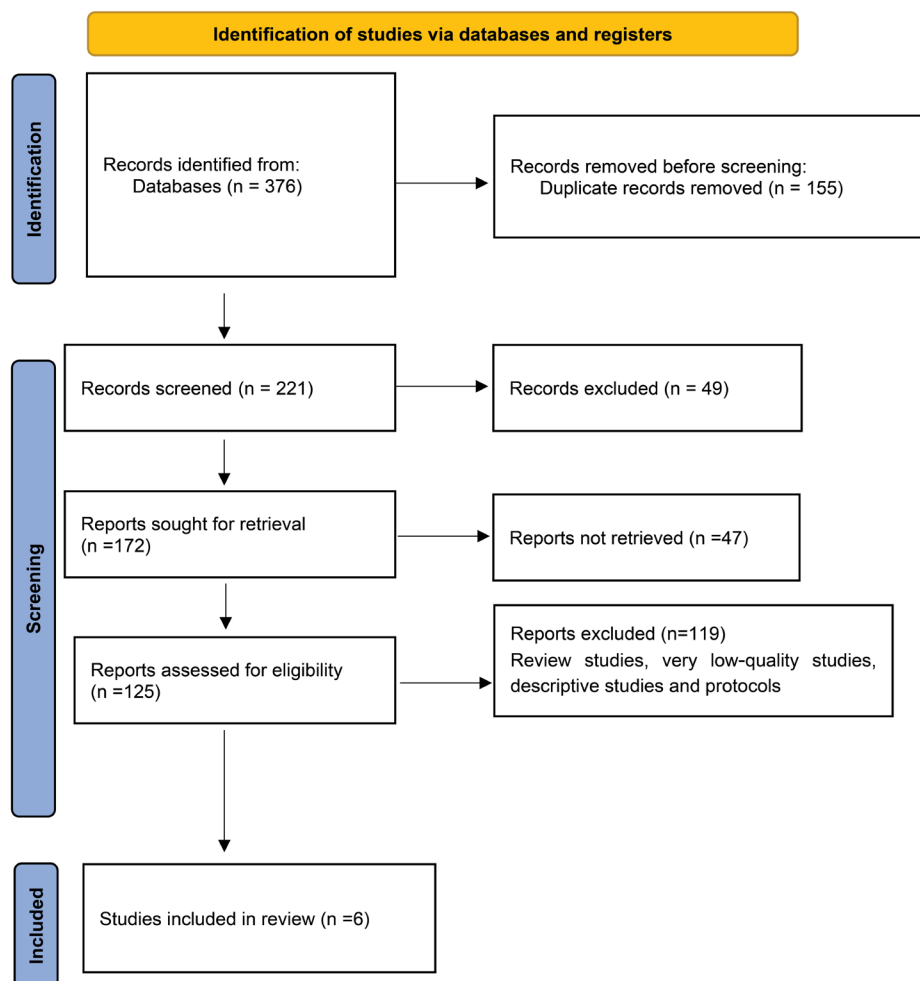

Figure 1. The flow chart of study selection (PRISMA).

Table 1. Specifications of articles which entered into the meta-analysis process

Authors name, year	Country	Type of Study	Total number	Mean age (y)	Number of people in SGLT2i group	Mean age in SGLT2i group	Number of people in compare group	Mean age in compare group	Compared group	During the study period
Anan G, 2023 (Men) (19)	Japan	Cross-sectional	1109212	NR	3731	NR	23845	NR	Other anti-diabetic drugs	January 1, 2021, to December 31, 2021
Anan G, 2023 (Women) (19)	Japan	Cross-sectional	762217	NR	1163	NR	11339	NR	Other anti-diabetic drugs	January 1, 2021, to December 31, 2021
Li Y, 2023(20)	USA	Cohort	116506	72	1128	NR	NR	NR	DPP4i	2017-2018
Paik JM, 2022(21)	USA	Cohort	662056	NR	331028	61.77	331028	61.67	DPP4i	2013-2020
Paik JM, 2022(21)	USA	Cohort	716406	NR	358203	64.4	358203	61.43	GLP1RA	2013-2020
Anan G, 2022 (Men)(1)	Japan	Cross-sectional	909628	≥ 20	105433	≥ 20	804195	≥ 20	Other anti-diabetic drugs	from January 2020 to December 2020
Anan G, 2022 (Women) (1)	Japan	Cross-sectional	628570	≥ 20	52637	≥ 20	575933	≥ 20	Other anti-diabetic drugs	from January 2020 to December 2020
Balasubramanian P, 2022(22)	USA	Randomized placebo-controlled trials	15081	NR	10177	NR	4904	59.5	Placebo	NR
Kristensen KB, 2021(10)	Denmark	Cohort	43866	≥ 40	24290	≥ 40	19576	≥ 40	GLP1RA	November 2012 to December 2018

NR: Not reported; GLP1RA: Glucagon-like peptide 1 receptor agonist; DPP4i: Dipeptidyl peptidase IV inhibitors.
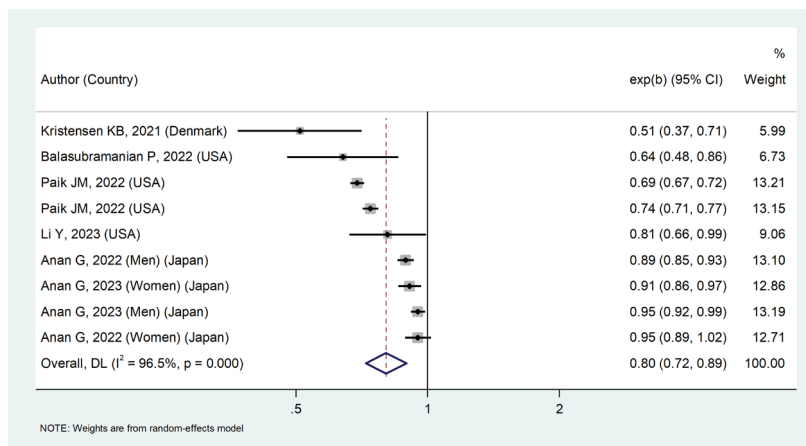
Figure 2. Forest plot of the association between SGLT2i intake and kidney stones.
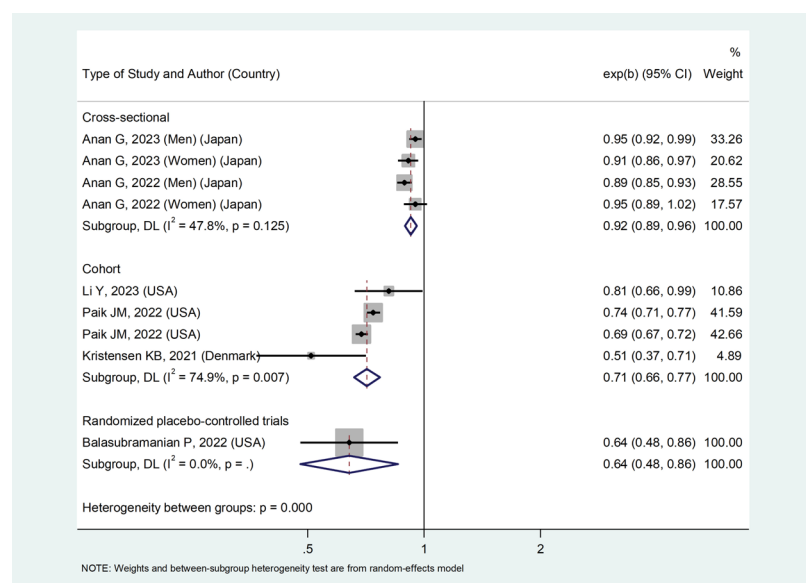

Figure 2. Forest plot of the association between SGLT2i intake and kidney stones by type of studies.

other antidiabetic drugs (OR = 0.92, 95% CI: 0.89, 0.9), and placebo (OR = 0.64, 95% CI: 0.48, 0.86) (Figure 4).

SGLT2 inhibitors administration in high-quality (OR = 0.81, 95% CI: 0.71, 0.93) and low-quality (OR = 0.81, 95% CI: 0.70, 0.94) studies reduced the risk of kidney calculi in consumers, and the result obtained from both groups (high-quality and low-quality) were similar (Figure 5).

Since race is a significant factor in kidney stone disease, our reviews were based on the countries. Results indicated that SGLT2 use in Japan (OR = 0.92, 95% CI: 0.89, 0.96), United States (OR = 0.72, 95% CI: 0.67, 0.76), and Denmark (OR = 0.51, 95% CI: 0.37, 0.71) prevented the kidney stone disease. The highest and lowest effects of SGLT2 inhibitors in kidney calculi prevention were observed in Japan and Denmark, respectively (Figure 6).

Additional analysis

The Meta-regression chart indicated no statistically significant relationship between the 'effect of SGLT2 inhibitors treatment on kidney calculi' and the number of studies' sample size ($P = 0.056$). In other words, the sample size did not affect the final result of our meta-analysis (Figure 7).

Figure 8 shows no publication bias in the present study ($P = 0.0957$), meaning no bias in searching the sources. The studies that reported SGLT2 inhibitors treatment effective in kidney stone disease prevention had a similar chance for publication as those that found no relationship between SGLT2 inhibitors and kidney calculi and were published. In this study also, we searched every related study without being biased in favor of the primary study hypothesis.

Discussion

After combining six studies with a total sample size of 4 963 542 individuals, we concluded that SGLT2 inhibitors
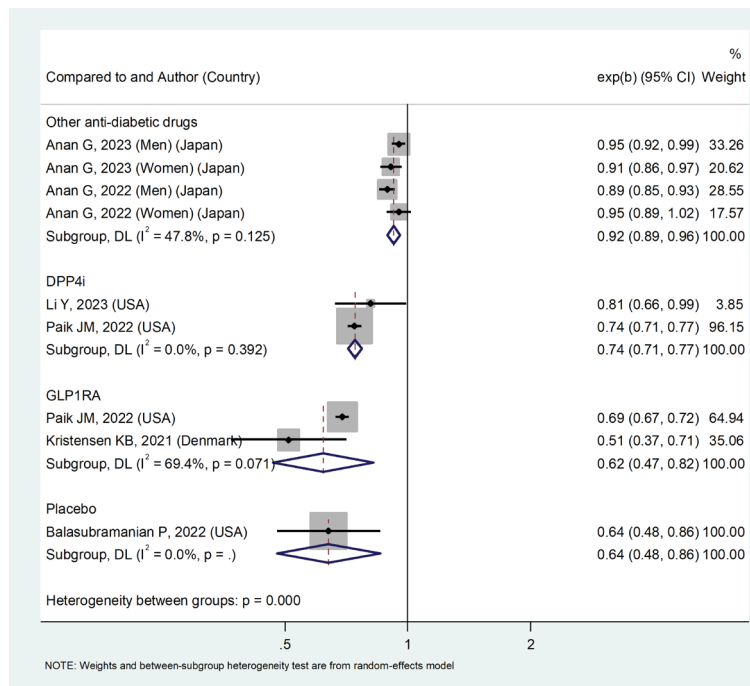
Figure 4. Forest plot of the association between SGLT2i intake and kidney stones by compare group.
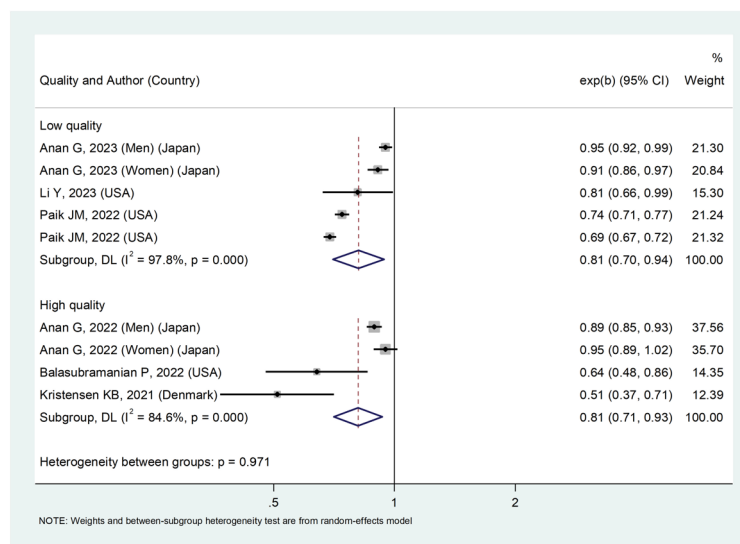

Figure 5. Forest plot of the association between SGLT2i intake and kidney stones by quality of studies.

administration had a preventive role in kidney stone disease and reduced the risk of kidney calculi by 20%. The results of a meta-analysis by Cosentino et al indicated no relationship between SGLT2 inhibitors and nephrolithiasis (OR: 0.85; 95% CI: 0.57–1.26) (23), which was not consistent with our study. However, the previous meta-analysis reviewed clinical trials published before 2018. On the other hand, our study reviewed observational studies and clinical trials published until 2023. The differences between the reviewed studies by the two meta-analyses may have caused the inconsistency between the results of the study by Cosentino et al and the present study.

Results of another meta-analysis by Menne et al indicated that SGLT2 inhibitors reduced the possibility of acute renal failure up to 36% (OR: 0.64; 95% CI: 0.53–0.78) (24). A meta-analysis of nine studies by Yu et al reported that despite SGLT2 inhibitors did not affect the eGFR level, they reduced the urine albumin/creatinine ratio. These inhibitors also reduced the incidence rate of acute renal failure in diabetes patients by up to 20% (OR: 0.80; 95% CI: 0.66-0.98) (25). Bae et al reviewed 48 studies in a meta-analysis to investigate the effect of SGLT2 inhibitors on the renal consequences of type-2 diabetes
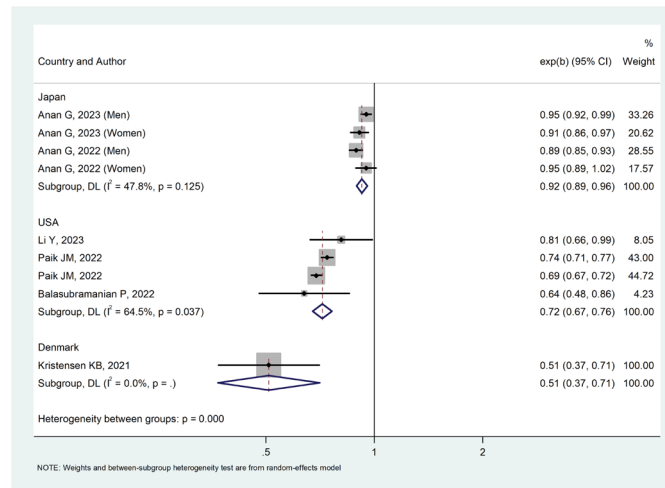
Figure 6. Forest plot of the association between SGLT2i intake and kidney stones by countries.

patients. They concluded that SGLT2 inhibitors reduced the risk of microalbuminuria (RR: 0.69; 95% CI: 0.49-0.97), macroalbuminuria (RR: 0.49; 95% CI: 0.33-0.73]), deterioration of nephropathy (RR: 0.73; 95% CI: 0.58 - 0.93), and risk of ESRD compared with the control group (RR: 0.70; 95% CI: 0.57-0.87) (26).
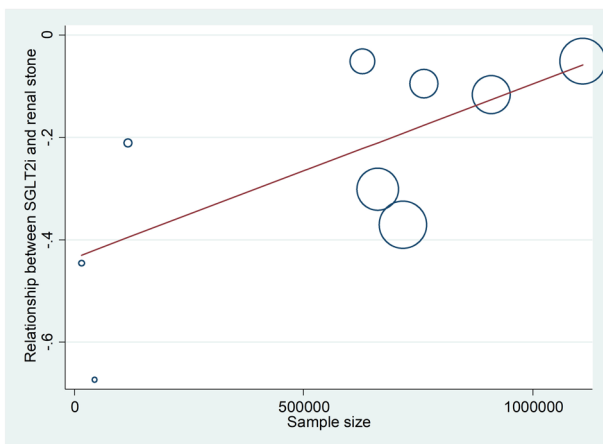

Figure 7. Meta-regression diagram of the relationship between "the effect of SGLT2 inhibitors on kidney stones" and the number of study samples

Figure 8. Publication bias chart.

In a recent meta-analysis which conducted on 34 studies, by Forbes et al compared with other antidiabetic drugs, SGLT2 inhibitors reduced the risk of renal failure by 46% (HR: 0.54; 95% CI: 0.47–0.63) (27). In a meta-analysis by Neuen et al, SGLT2 inhibitors administration reduced the risk of dialysis, transplant, or death from renal disease (RR: 0.67; 95% CI: 0.52-0.86), risk of end-stage renal failure (RR: 0.65 [95% CI: 0.53-0.81]), and acute renal failure (RR: 0.75; 95% CI: 0.66-0.85) (28). The results of the mentioned studies were consistent with the present meta-analysis. These studies showed that besides controlling the blood sugar level, SGLT2 inhibitors also effectively reduced the risk of renal diseases, including end-stage renal failure, kidney failure, renal consequences, and acute renal injury. In this study, we concluded that SGLT2 inhibitors reduced the risk of kidney calculi. Therefore, it appears that SGLT2 inhibitors are a suitable candidate for diabetic patients who suffer renal complications.

Conclusion

SGLT2 inhibitors administration reduced the risk of kidney calculi in the entire users, men, and women, by 20%, 8%, and 7%, respectively. Furthermore, SGLT2 inhibitors treatment prevented kidney calculi in cross-sectional studies by 8%, cohort studies by 29%, RCTs by 36%, high-quality studies by 19%, low-quality studies by 19%, Japan by 8%, United States by 28%, Denmark by 49%, compared with DPP4i by 26%, compared with GLP1RA by 38%, compared with other antidiabetic drugs by 8%, and compared with placebo by 36%. These results indicated that compared with other antidiabetic drugs and placebo, SGLT2 inhibitors generally have better function in diabetic patients facing the risk of nephrolithiasis, and they prevent kidney calculi. However, considering the low number of reviewed studies, it appears that more studies are required on this subject to confirm the results obtained from this meta-analysis.

Limitations of the study

The reviewed studies did not specify the type of the administered SGLT2 inhibitor drug or the administered dose; accordingly, we could not evaluate the effect of different types of SGLT2 inhibitors (such as dapagliflozin, empagliflozin, and canagliflozin) on nephrolithiasis, and compare the effects of high and low doses of SGLT2 on the kidney calculi.

Among the reviewed studies, only two reported the effect of SGLT2 inhibitors on the kidney calculi by patients' gender. Additionally, SGLT2 inhibitor treatment lowered the risk of kidney calculi by 20% for the entire patient population, however in men and women, it prevented 8% and 7%, respectively. In other words, the general outcome for male patients was relatively different than for female patients. Some studies did not report the age groups, but others defined age ranges. Therefore, while age is a significant factor for kidney calculi incidence, it was not possible to evaluate the effect of SGLT2 inhibitors on different age groups. We recommend addressing these limitations in future studies to reduce the heterogeneity and achieve more accurate results.

Authors' contribution

Conceptualization: Ramin Haghighi and Mahdi Behi.
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Investigation: Ali Rahnama Sisakht and Mohammad Mehdi Darzi.
Methodology: Hossein Mardanparvar and Parvin Kamkar
Project management: Ramin Haghighi.
Resources: All authors.
Supervision: Ali Rahnama Sisakht.
Validation: Farshad Gharebakhshi.
Visualization: Mohammad Hamidi Madani.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023483132) and Research Registry website (Unique Identifying Number (UIN) reviewregistry1743). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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