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Association between SGLT2 (sodium-glucose cotransporter-2) inhibitors and bladder cancer in individuals with type 2 diabetes; a systematic review and meta-analysis

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ABSTRACT

Introduction: Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the most recent pharmaceutical group for type 2 diabetes (T2D) treatment. Evidence indicates contradictory relationships between sodium-glucose cotransporter-2 inhibitors and bladder cancer (BC). Hence, this study aims to investigate the relationship between SGLT2 inhibitors and BC in patients with T2D.

Materials and Methods: This study is a systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). International databases including Cochrane, Web of Science, Scopus, PubMed, and Google Scholar were conducted for searching with keywords and without time and language limitations. The reference searching stage continued upgrading until November, 2022. Data analysis was performed with STATA 14 software. The tests with *P* values lower than 0.05 were considered statistically significant.

Results: The four reviewed studies with a sample size comprising 497 755 individuals indicated the impact of SGLT2 inhibitors on BC of patients with T2D (OR: 0.68; 95% CI: 0.37, 1.2). The effect of dapagliflozin, canagliflozin and empagliflozin administration on the incidence of BC among the T2D patients were (OR: 0.72; 95% CI: 0.39, 1.30), (OR: 0.53; 95% CI: 0.23, 1.20), and (OR: 0.51; 95% CI: 0.20, 1.28), respectively.

Conclusion: The general conclusion of this study revealed that SGLT2 inhibitors did not increase the risk of BC in T2D patients. The analysis of subgroups also indicated that the administration of dapagliflozin, canagliflozin, and empagliflozin also did not increase the risk of BC in T2D patients.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID=CRD42023389014).

Meta-analysis

Implication for health policy/practice/research/medical education:
This systematic review and meta-analysis was conducted with the aim of investigation of the relationship between SGLT2 (sodium-glucose cotransporter-2) inhibitors and bladder cancer in individuals with type 2 diabetes (T2D). This study showed that these agents did not increase the risk of bladder cancer in T2D patients. The analysis of subgroups also indicated that the administration of dapagliflozin, canagliflozin and empagliflozin did not increase the risk of bladder cancer in type 2 diabetes patients..

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Introduction

Epidemiological evidence indicates that cases with diabetes are exposed to higher risks of cancer (1). Sodium-glucose cotransporter-2 inhibitors (SGLT2i), such as empagliflozin, canagliflozin, and dapagliflozin, are the most recent pharmaceutical group for type 2 diabetes (T2D) treatment. These pharmaceuticals were introduced in 2013 and gained significant popularity due to lower risks of hypoglycemia, lack of adverse effects, and neutral effects on body weight compared with previous antidiabetic medicines (2,3). Following the pioglitazone, SGLT2i inhibitors were introduced as a new group of oral anti-hyperglycemic agents effective for T2D treatment. This group reduces glucose absorption in the kidneys, increases glucosuria and reduces blood glucose levels (4).

Besides the decline of blood glucose level, there are extensive advantages related to the administration of SGLT2 inhibitors for T2D patients, including a significant decrease of hemoglobin A1c and major adverse cardiovascular events (MACE), reduction of end-stage renal disease (ESRD) compared with placebo (5,6). SGLT2i application also reduced body weight, blood pressure, and mortality rate (7-10).

There are concerns that SGLT2 inhibitors may increase the risk of bladder cancer (BC). Following the administration of first generation of this class, such a relationship was indicated. Additionally, the meta-analysis of randomized clinical trials demonstrated the same results (11); however, the findings are inconsistent (12). Accordingly, this study aims to investigate the relationship between the SGLT2 inhibitors and the risk of BC in patients with T2D. In this study, we will combine the inconsistent results of the previous studies using the systematic review method and meta-analysis, and we will investigate the relationship between the different SGLT2 inhibitors with BC of cases with T2D.

Materials and Methods

Study design

The present study is a systematic review and meta-analysis investigating the relationship between SGLT2 inhibitors and BC among patients with T2D.

Search strategy

International databases including Cochrane, Web of Science, Scopus, PubMed and Google Scholar were conducted to search with standard keywords without language limitations and to use Medical Subject Headings (MeSH). The keywords conducted in the study included cancer, neoplasm, diabetes, SGLT2, sodium/glucose cotransporter 2, dapagliflozin, canagliflozin, empagliflozin and bladder.

The reference searching stage continued upgrading until November, 2022. Combined keywords were also searched using OR and AND operators in the mentioned databases. The primary studies retrieved at this stage entered EndNote 9 software so we could quickly identify the duplicate studies until one study remained from each repeated study group. Then for manually searching the references, the obtained list of references was reviewed at the end of the primary studies. The inquiry strategy of PubMed; (((SGLT2 OR sodium/glucose cotransporter 2 OR Dapagliflozin OR Canagliflozin OR Empagliflozin) AND (Cancer OR Neoplasm)) AND (Bladder)) AND (Diabetes).

PICO (population, intervention, comparison, outcome) components

Patients: T2D patients, Intervention: SGLT2 inhibitors, Comparison: a group of diabetic patients who used other antidiabetic medications to control their blood sugar levels, Outcome; incidence of BC.

Inclusion criteria

Studies that had investigated the role of SGLT2 inhibitors in the incidence of BC among T2D patients entered the meta-analysis.

Exclusion criteria

Studies that lacked sufficient data for analysis, those that had investigated the role of SGLT2 inhibitors in addition to another pharmaceutical agent, studies which had assessed the relationship between SGLT2 inhibitors and incidence of cancers other than BC, and the studies that their full texts were not available, and also low-quality studies, and finally reports of case studies were excluded from this meta-analysis.

Qualitative assessment

We used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for the observational studies. STROBE consists of 22 sections that cover various parts of a report. In this checklist, the sum of scores was determinative. Hence, scores 1 to 15 indicate low-quality, 16 to 30 indicate moderate, and 31 to 44 indicate supreme quality. The current study's cutoff point was a score of 15 (13). After evaluating studies based on the STROBE checklist, the third researcher settled the disputes between the two reviewers.

Data extraction

To reduce the risk of bias in the reports and to minimize the errors in data collection, the two researchers separately extracted the data from the studies. The researchers entered the data into a checklist, including the researchers' names, type of study, mean age, sample size, year, country

and the relative risk between the SGLT2 inhibitors and BC. The third researcher assessed the extracted data to resolve the inconsistencies.

Statistical analysis

The odds ratio (OR) measure was used to investigate the relationship between the SGLT2 inhibitors and BC among T2D patients. The odds ratio logarithm was used for combining the study results, and the I^2 index and Cochran (Q) test were used to investigate the between-study heterogeneity. Due to the high heterogeneity of this study ($I^2 = 98.2\%$), the random effects model was used. The data analysis was conducted using STATA 14 software. The p-values lower than 0.05 were considered as the tests' significance level.

Results

Selection of investigations

In the first stage, inquiry at the mentioned databases led to the identification of 211 articles. After investigating the titles of the studies, 95 duplicate studies were deleted. The abstract of the 116 remaining studies was reviewed, and based on the exclusion criteria, 112 articles were removed from the study. Finally, the four remaining investigations entered the qualitative consideration stage. All four studies had good qualities and entered the meta-analysis (Figure 1).

Table 1 presents a summary of the most important basic information about the reviewed studies.

Among the four reviewed studies with a total sample size comprising 497755 individuals, one was a case-control study, and three were cohort studies. The articles were published in 2021 and 2022. In the group of cohort studies, the effect of SGLT2 inhibitors on BC among the patients with T2D indicated OR: 0.95; 95% CI: 0.89, 1.02, which was not statistically significant. However, in the group of case-control studies, the effect of SGLT2 inhibitors on BC among the patients with T2D indicated OR: 0.20; 95% CI: 0.17, 0.24, which this relationship was statistically significant. Regarding the entire study also, the findings indicated OR: 0.68; 95% CI: 0.37, 1.24. In other words, the SGLT2 inhibitors did not increase the risk of BC among the patients with T2D (Figure 2).

Subgroup analysis

We separately reviewed the results of various SGLT2 inhibitor classes for a more accurate investigation of the relationship between the SGLT2 inhibitors and the

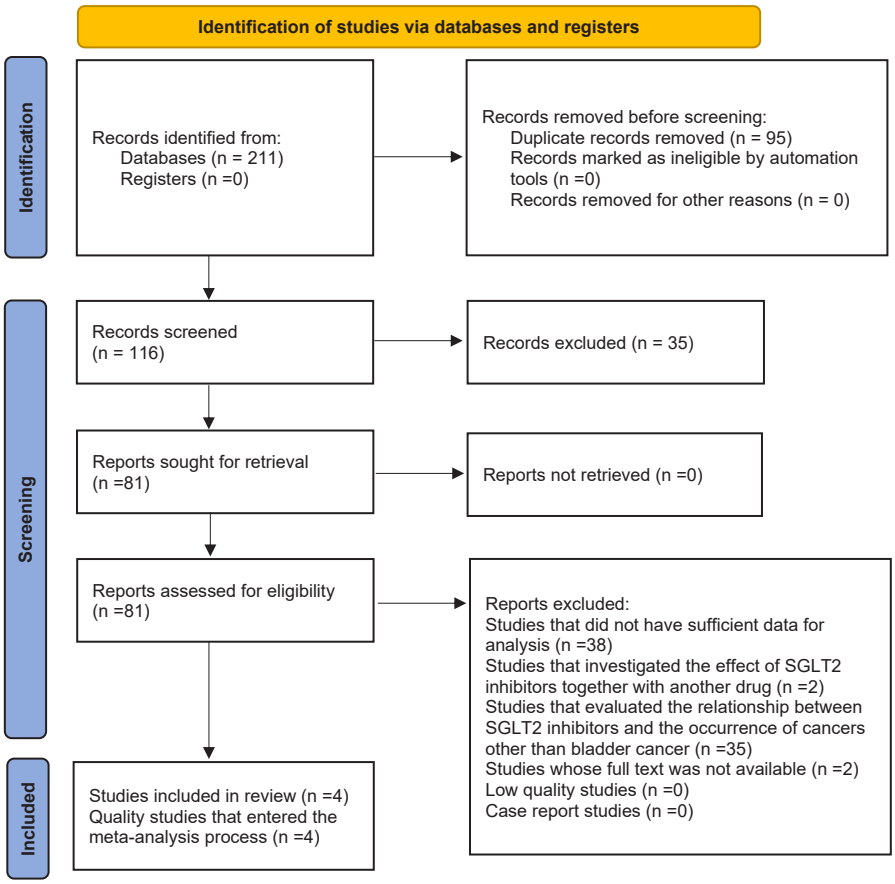

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed studies

Author, year of publication	Place	Type of Study	Compare group	Sample size	Mean age (year)	OR of SGLT2 on Bladder cancer	Low limit -OR of SGLT2 on Bladder cancer	Up limit-OR of SGLT2 on Bladder cancer
Garcia M, 2021(14)	European Economic Area	Case-Control	Other Anti diabetic Agents	155	65.6	0.2	0.17	0.24
Li YR, 2021(15)	Taiwan	Cohort	Pioglitazone	3359	50.3	0.49	0.05	4.94
Abrahami D, 2022(16)	USA, UK	Cohort	GLP-1	347059	61.8	0.9	0.81	1
Abrahami D, 2022(16)	USA, UK	Cohort	DPP4	347059	61.1	0.99	0.91	1.09
Ueda P, 2022(17)	Sweden	Cohort	GLP-1	57383	-	1.24	0.72	2.13
Ueda P, 2022(17)	Denmark	Cohort	GLP-1	89799	-	0.78	0.32	1.88

incidence of BC among patients with T2D. We classified the studies into three groups; the effect of dapagliflozin, canagliflozin, and empagliflozin administration on BC incidence among the T2D patients were 'OR: 0.72; 95% CI: 0.39, 1.30,' 'OR: 0.53; 95% CI: 0.23, 1.20,' and 'OR: 0.51; 95% CI: 0.20, 1.28,' respectively. None of the mentioned relationships were statistically significant. Finally, the general result was confirmed, and the analysis of subgroups revealed that dapagliflozin, canagliflozin, and empagliflozin medications did not increase the risk of BC among T2D patients (Table 2).

In Figure 3, the publication bias chart indicated that the reference search stage was completed. In other words, the positive and negative results had an equal chance of publication, and the researchers were not biased in searching the references. Finally, the publication bias in this meta-analysis was not statistically significant ($P = 0.669$).

Discussion

The reviewed studies investigated 497755 patients with T2D. In this systematic review and meta-analysis, we realized that SGLT2 inhibitors did not increase the risk of BC compared with other antidiabetic medications.

A previous meta-analysis by Dicembrini et al aimed to investigate the effects of SGLT-2i on the general incidence of malignancies and various types of cancers using 27 clinical trials did not indicate any difference in the malignancy incidence between the patients dedicated to SGLT-2i and the control group (H-OR: 0.98 (0.77-1.24)). As a result, the incidence of BC or other forms of cancer did not increase after the treatment with SGLT-2i agents (12). In the review study by Pelletier et al, SGLT2 inhibitors did not increase cancer risk compared with placebo and active comparators. However, the researchers believed they required additional evidence to comment confidently on this subject (18). The result of the two

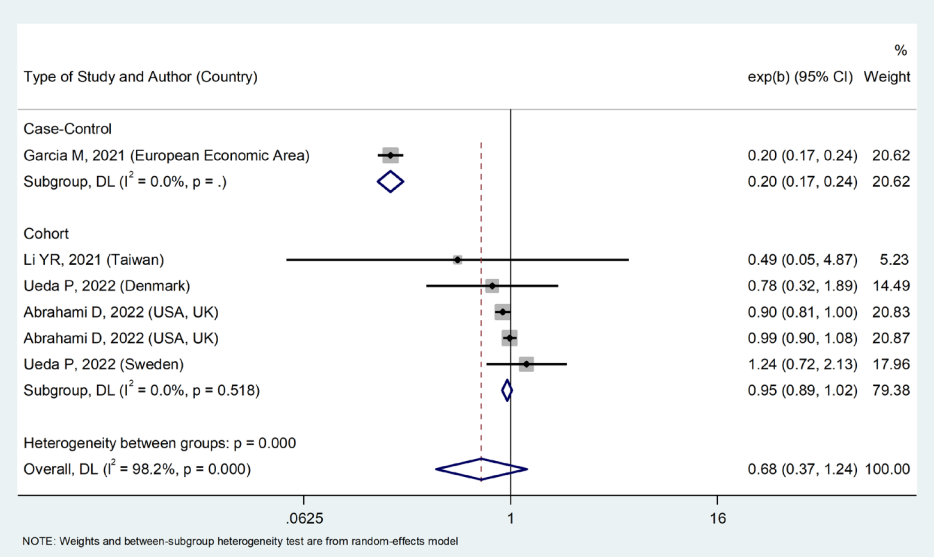

Figure 2. Forest plot showing the impact of SGLT2 on bladder cancer in diabetic patients.

Table 2. Relationship between SGLT2 inhibitors and bladder cancer incidence in type 2 diabetes patients, by drug type

Subgroups	OR	95% CI		I^2 (%)	*P* value
		Low	Up		
Dapagliflozin	0.72	0.39	1.30	95.5	<0.001
Empagliflozin	0.51	0.20	1.28	98.4	<0.001
Canagliflozin	0.53	0.23	1.20	97.9	<0.001

OR: odds ratio, Low: low limit, Up: up limit.

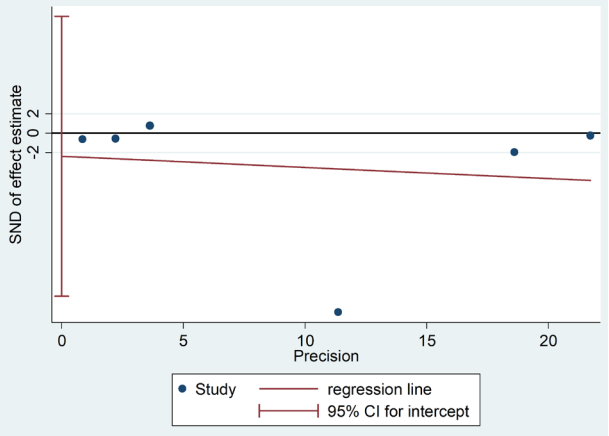

Figure 3. Publication bias.

studies were consistent with these findings and confirmed our results.

The results of a recent meta-analysis by Benedetti et al, indicated that SGLT-2i significantly reduced the general cancer risk compared with the placebo (RR = 0.35, CI 0.33–0.37, *P* = 0. 00), and dapagliflozin had the highest efficacy (RR = 0. 06, CI 0.06–0. 07) (19). The mentioned study indicated the preventative and conservative effect of SGLT-2i on cancer incidence, which is not consistent with the result of the current meta-analysis. The extensive diversity of cancers may be one of the causes of this inconsistency because we only investigated BC; however, the mentioned study reviewed every type of cancer.

The results of a meta-analysis by Tang et al indicated that compared with placebo or other forms of active glucose reducer medications, SGLT2 inhibitors did not significantly increase the risk of cancer (OR 1.14, 95% CI 0.96-1.36). However, the analysis of subgroups based on different types of cancer indicated that SGLT2 inhibitors might increase the risk of BC (OR 3.87, 95% CI 1.48-10.08]), especially empagliflozin (OR 4.49, 95% CI 1.21-16.73) (11). However, in the current study, empagliflozin did not increase the risk of BC (similar to other SGLT2 inhibitors). Sometimes the SGLT2 inhibitors increase the risk of genitourinary tract infections; hence, physicians may perform more diagnostic measures for chronic urinary infection follow-up, which may have eventually led to the diagnosis of BC. Nevertheless, BC may have progressed before the administration of SGLT2 inhibitors. Nonetheless, we have to be cautious. Consequently, we require more studies with higher quality and greater sample size to determine the relationship between the SGLT2 inhibitors and BC of patients with T2D.

The limitation on the number of reviewed studies, the impossibility of presenting the results according to variables including age and gender of patients, drug dosage, and duration of treatment, different nature of reviewed studies, and difference of the antidiabetic drugs used for the control group are among the limitations of the study.

Conclusion

This study indicated that compared with other antidiabetic medications, the sodium-glucose cotransporter-2inhibitors did not increase the risk of BC in patients with T2D. The analysis of subgroups also revealed that dapagliflozin, canagliflozin, and empagliflozin did not increase the risk of BC in patients with T2D, and none of them is risk factors for BC. Considering the previous studies, we recommend more research in this field to overcome the limitations and obstacles of the current study. Hence, the researchers can investigate the effect of SGLT2 inhibitors on BC by separating the SGLT2 inhibitor types, patients' gender, age group, dosage, and duration of drug administration. With further studies, we can overcome this challenge and assess the relationship between SGLT2 inhibitors and BC among T2D patients more confidently and accurately.

Authors' contribution

Conceptualization: MM and AF.
Methodology: ESh, MKh and HM.
Validation: NP and EZ.
Formal Analysis: ZA and SM.
Research: AR and SM.
Resources: EZ, AF and ZA.
Data Curation: ESh and MKh.
Writing—Original Draft Preparation: HM, MM and NP.
Writing—Reviewing and Editing: HM, ZA and AF.
Visualization: EZ and AR.
Supervision: MM.
Project Management: HM.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by

the author. This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42023389014)

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