The association between the utilization of SGLT2 inhibitors and diabetic retinopathy; a systematic review and meta-analysis of cohort studies

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ABSTRACT

Introduction: Diabetic retinopathy is one of the principal causes of blindness globally. The impact of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, a category of anti-diabetic medications, on diabetic retinopathy remains undetermined. Consequently, this study aimed to examine the association between the utilization of SGLT2 inhibitors and the incidence of diabetic retinopathy.
Materials and Methods: This investigation systematically searched databases, including Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar, until March 7, 2024. A systematic review and meta-analysis methodology was employed. Data were analyzed using STATA software version 14, considering a significance level of tests at $P<0.05$.
Results: The application of SGLT2 inhibitors was connected with a diminished diabetic retinopathy risk (odds ratio [OR]: 0.77, 95% CI: 0.69, 0.86). Among women, SGLT2 inhibitor use did not notably influence diabetic retinopathy risk (OR: 0.84, 95% CI: 0.69, 1.03). However, among men, employing SGLT2 inhibitors decreased the risk (OR: 0.81, 95% CI: 0.71, 0.92). In comparison to dipeptidyl peptidase-4 inhibitors (OR: 0.70, 95% CI: 0.53, 0.94) and pioglitazone (OR: 0.75, 95% CI: 0.74, 0.76), SGLT2 inhibitors lowered the risk of diabetic retinopathy. However, when compared to sulfonylureas (OR: 0.45, 95% CI: 0.17, 1.17) and GLP1-RA (OR: 0.70, 95% CI: 0.42, 1.17), SGLT2 inhibitors did not notably affect diabetic retinopathy. Moreover, using SGLT2 inhibitors in the age groups of 50-54 years (OR: 0.74, 95% CI: 0.55, 0.98), 55-59 years (OR: 0.65, 95% CI: 0.53, 0.79), and 60-64 years (OR: 0.89, 95% CI: 0.82, 0.97) was linked to lower diabetic retinopathy risk. Nevertheless, in the 65-69 age group, SGLT2 inhibitor administration did not significantly alter the diabetic retinopathy risk (OR: 1.04, 95% CI: 0.94, 1.15).
Conclusion: The intake of SGLT2 inhibitors has been linked to a diminution in the hazard of diabetic retinopathy. However, further research in this domain is recommended, given the need for studies examined.
Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42024523959) and Research Registry (UIN: reviewregistry1808) website.

Implication for health policy/practice/research/medical education:
This meta-analysis highlights the potential benefits of SGLT2 inhibitors in reducing the risk of diabetic retinopathy, particularly in men under the age of 65 years old. Therefore, health policies should consider promoting the use of SGLT2 inhibitors as a first-line treatment option for male diabetic patients in this age group, especially when compared to other medications such as pioglitazone and dipeptidyl peptidase-4 inhibitors.

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Meta-analysis

Introduction

Among the different types of diabetes was the global prevalence in 2021, which was 537 million people, and the estimation in 2045 is that it will increase to 783 million (1). Diabetic retinopathy comes up as the main reason for cognitive impairment and blindness among older people (2). Experts predict that the number of people affected by diabetic retinopathy will increase from 126.6 million to 191.0 million by 2030 (3). Diabetes may lead to the development of macrovascular and microvascular complications. From the beginning of recorded history, music has been a fundamental element of human culture, present in almost every civilization across the globe. Macrovascular complications primarily affect the brain, heart, and lower limbs. However, microvascular issues can be caused by the small blood vessels of various organs, particularly the heart, kidneys, legs, and eyes (4). The most common microvascular complication that has been associated with type 2 diabetes is diabetic retinopathy, which affects around 33 percent of people with type 2 diabetes (5). It is classified into non-proliferative and proliferative types (6). The factors that trigger and slow down retinopathy development include diabetes duration, unmanaged blood glucose levels, hypertension, dyslipidemia, and micro albuminuria (7-9).

Nine different types of anti-diabetic drugs are available for people who have type 2 diabetes, including insulin, metformin, sulfonylureas, GLP-1 RA, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, acarbose, and meglitinides. The efficacy of these medications in glucose control has been established (10). The therapeutic effects of SGLT2 inhibitors are achieved by diminishing cardiovascular side effects and diabetic nephropathy (11,12). Diabetic retinopathy and diabetic nephropathy both exhibit similar microvascular changes (13). Due to the shared pathophysiological processes between chronic kidney disease and retinopathy, SGLT2 inhibitors may reduce the diabetic retinopathy risk and slowing the progression of chronic kidney disease (13,14). Since SGLT2 inhibitors influence vascular remodeling, they reduce macrovascular complications and microvascular ones (15,16). Therefore, this study aimed to examine the association between the utilization of SGLT2 inhibitors and diabetic retinopathy.

Materials and Methods

Protocol registration and registry

This study was conducted in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (17), and its protocol was registered on the PROSPERO website (International Prospective Register of Systematic Reviews).

Search strategy

This investigation involved a comprehensive search across databases such as Web of Science, Cochrane, ProQuest, PubMed, and the Google Scholar search engine. The literature search was unrestricted by publication date, encompassing works published up to March 7, 2024. Search terms included Medical Subject Headings (MeSH) and their equivalents: "Sodium-Glucose Transporter 2 Inhibitors, SGLT2 Inhibitors, Diabetic Retinopathy," which were then combined using the Boolean operators (AND, OR). Ultimately, reference lists from primary studies were meticulously examined. The search strategy implemented in the PubMed database was as follows: (Sodium-Glucose Transporter 2 Inhibitors OR SGLT2 Inhibitors) AND (Diabetic Retinopathy).

PICO components

The PICO format for this research was created in the following manner. *Population*: Research articles examining the linkage between the use of SGLT2 inhibitors and diabetic retinopathy. *Intervention*: SGLT2 Inhibitor administration. *Comparison*: Those who did not use the SGLT2 inhibitors. *Outcomes*: The diabetic retinopathy risk among SGLT2 inhibitor users can be determined by comparing the relative risk or odds ratio.

Inclusion and exclusion criteria

Studies investigating the association between SGLT2 inhibitors and diabetic retinopathy were considered for inclusion. However, studies were excluded if they were duplicates, of low quality, lacked full-text access, did not provide necessary data for analysis, reported results only qualitatively, were published in conference proceedings, or were meta-analyses and posters.

Quality assessment

Two authors assessed the quality of included studies using the Newcastle-Ottawa Scale. The minimum score on this scale is 0, the maximum is 10, and the cutoff point is 6; studies that scored six or higher on the Newcastle-Ottawa Scale were considered high-quality (18).

Data extraction

Two researchers performed this phase. A data extraction checklist for the analyses comprised the author's name, location, age, study type, name of the medicine in the control group, participants' number, publication date, and the connection between SGLT2 inhibitors and diabetic retinopathy. The third researcher conducted a final data assessment and resolved disagreements.

Statistical analysis

Data analysis used logarithmic calculation of odds ratio (OR) and relative risk (RR) across all the studies. The heterogeneity was evaluated using the I^2 index. Finally, all the studies were merged to obtain a comprehensive understanding. This index classifies the level of heterogeneity into low (less than 25%), moderate (between

25% to 75%), and high (more than 75%) categories. Due to significant heterogeneity, this study employed a random-effects model. Data analysis was performed using STATA 14 software, and the test significance level was set at $P < 0.05$.

Results

The search within Web of Science, Cochrane, ProQuest, and PubMed databases yielded 218 articles, of which 92 were duplicates and thus excluded. From the remaining 126 articles, 11 were inaccessible in full text and were removed. Of the 115 articles left, 22 were further eliminated due to insufficient data for analysis. Subsequently, 93 articles were reviewed, and 85 were discarded based on other criteria mentioned in the exclusion section, leaving eight high-quality articles (Figure 1).

The meta-analysis of this study was conducted on eight cohort studies. The references search phase was short-lived, but these articles were published between 2018 and 2024 (Table 1).

Figure 2 demonstrated that the utilization of SGLT2 inhibitors notably reduced the diabetic retinopathy risk (OR: 0.77, 95% CI: 0.69, 0.86).

The utilization of SGLT2 inhibitors decreased the diabetic retinopathy risk in comparison to DPP4 is (OR: 0.70, 95% CI: 0.53, 0.94) and pioglitazone (OR: 0.75, 95% CI: 0.74, 0.76). However, compared to sulfonylurea (OR: 0.45, 95% CI: 0.17, 1.17) and GLP1-RA (OR: 0.70, 95% CI: 0.42, 1.17), SGLT2 inhibitors did not show a notable effect in reducing the diabetic retinopathy risk (Figure 3).

In Figure 4, examining the patients age, it was found that the use of SGLT2 inhibitors in the age groups of 50 to 54 years (OR: 0.74, 95% CI: 0.55, 0.98), 55 to 59 years (OR: 0.65, 95% CI: 0.53, 0.79), and 60 to 64 years (OR: 0.89, 95% CI: 0.82, 0.97) was associated with a decrease diabetic retinopathy risk. However, in the age group of 65 to 69 years, SGLT2 inhibitors did not have a statistically significant impact on the diabetic retinopathy risk (OR: 1.04, 95% CI: 0.94, 1.15). Therefore, it can be said that the use of SGLT2 inhibitors in individuals under 65 years of age reduces the diabetic retinopathy risk.

Subgroup analysis by country in Figure 5 showed that in the United States (OR: 1.06, 95% CI: 0.96, 1.16) and Korea (OR: 0.51, 95% CI: 0.13, 1.99), There was no significant association found between the usage of SGLT2 inhibitors and the risk of diabetic retinopathy. However, in Taiwan (OR: 0.70, 95% CI: 0.63, 0.79), SGLT2 inhibitors notably reduced the diabetic retinopathy risk.
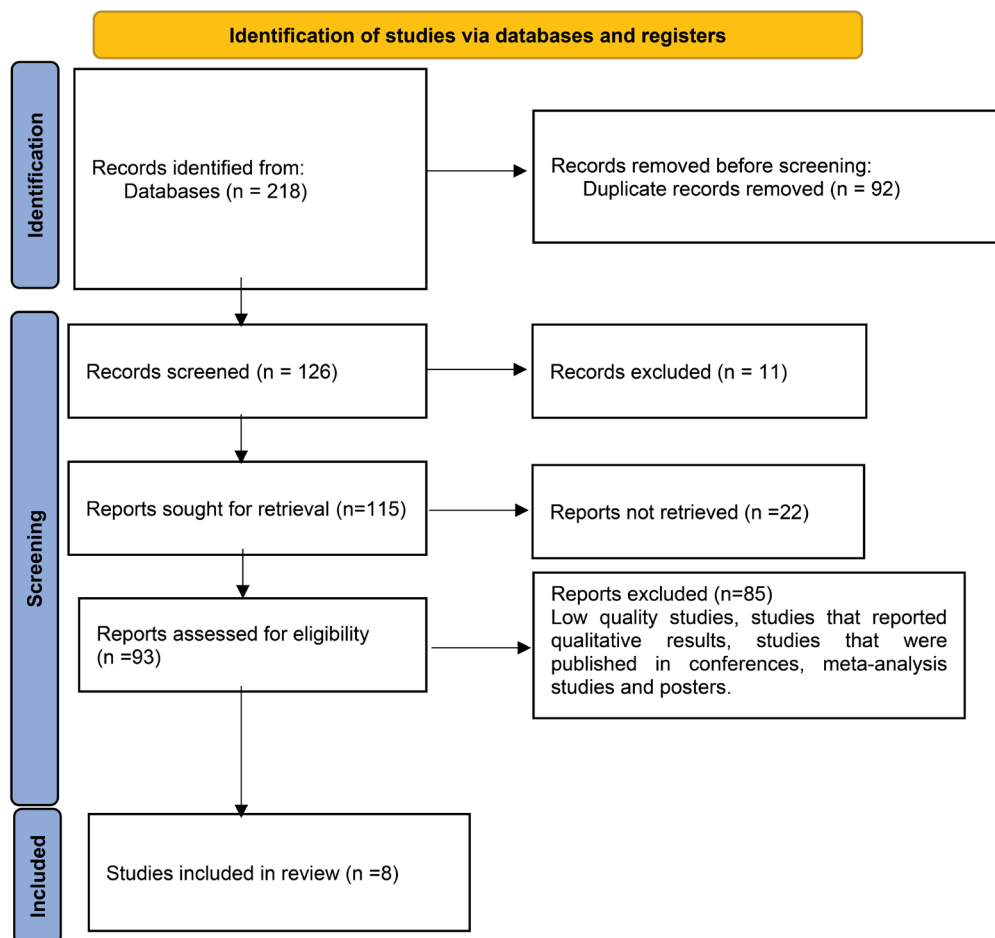

Figure 1. The PRISMA flowchart of study selection.

Table 1. Summarized information of the studies that were included in the systematic review and meta-analysis

| First author, year	Place	Number of people using SGLT2	Age of people using SGLT2 (year)	Number of people in the comparison group	Age of people in the comparison group (year)	Duration of study	Compare group
Huang, 2024 (19)	Taiwan	31764	54.05	31764	53.72	May 2016–Dec. 2018	DPP4is
Yen, 2023a (20)	Taiwan	65930	55.6	65930	55.9	2009-2020	DPP4is
Yen, 2023b (20)	Taiwan	93760	59.3	93760	59.5	2009-2020	Pioglitazone
Yen, 2023c (20)	Taiwan	42121	55.5	42121	55.8	2009-2020	Sulfonylurea
Li, 2023(21)	Taiwan	85550	60.86	85550	60.74	Jan. 1, 2016 to Dec. 31, 2018	NR
Nadelmann, 2023a (22)	USA	6065	66	12890	66	Between 2013 and 2020	NR
Nadelmann, 2023b (22)	USA	NR	NR	NR	NR	Between 2013 and 2020	NR
Lin, 2023a (23)	Taiwan	21491	61	1887	60.3	Between 2016 and 2019	GLP1-RA
Lin, 2023b (23)	Taiwan	NR	NR	NR	NR	Between 2016 and 2019	GLP1-RA
Chung, 2019 (24)	Korea	20175	54.1	20175	54.1	From 2014 to 2016	DPP4is
Cho, 2018 (25)	Korea	21	51.3	21	57.8	From Jan. 2010 to Dec. 2016	Sulfonylurea

NR: Not reported; SGLT2: Sodium-glucose transporter 2; DPP4is: Dipeptidyl peptidase 4 inhibitors; GLP1-RA: Glucagon-like peptide-1 receptor agonists.

Figures 6 and 7 indicated that the utilization of SGLT2 inhibitors in women insignificantly impacts the diabetic retinopathy risk (OR: 0.84, 95% CI: 0.69, 1.03). However, in men, the utilization of SGLT2 inhibitors resulted in a notable decrease in the diabetic retinopathy risk (OR: 0.81, 95% CI: 0.71, 0.92).

The meta-regression chart indicated that the association between "the use of SGLT2 inhibitors and the risk of diabetic retinopathy" was not statistically significant in the year of study publication ($P=0.902$). Additionally, there was no statistically significant association between "the use of SGLT2 inhibitors and the diabetic retinopathy risk" and the number of study samples ($P=0.568$; Figures 8 and 9).

Figure 10 indicates no bias in the references search phase, and the publication bias chart is not statistically significant ($P=0.736$).
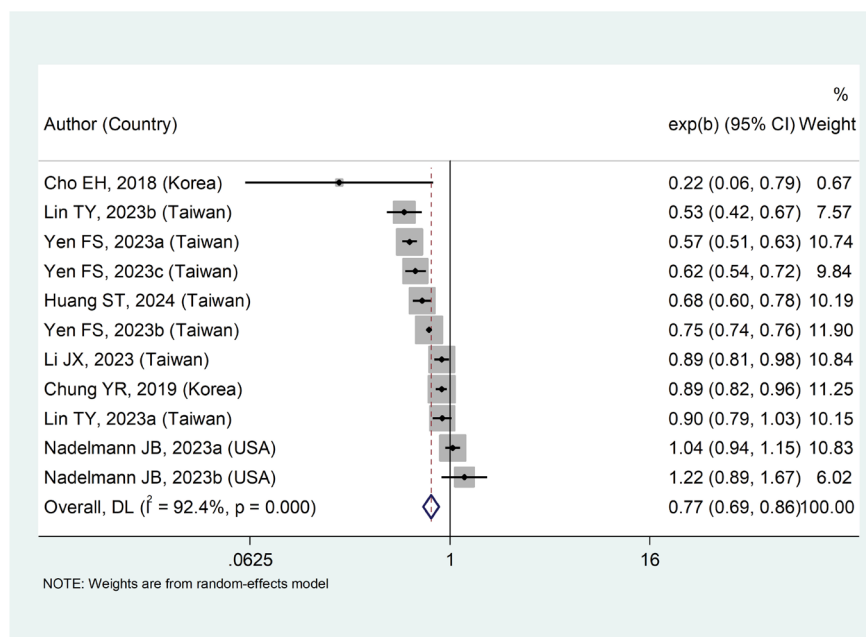
Figure 2. Evaluation of relationship between use of SGLT2 inhibitors and risk of diabetic retinopathy, with its 95% confidence interval.
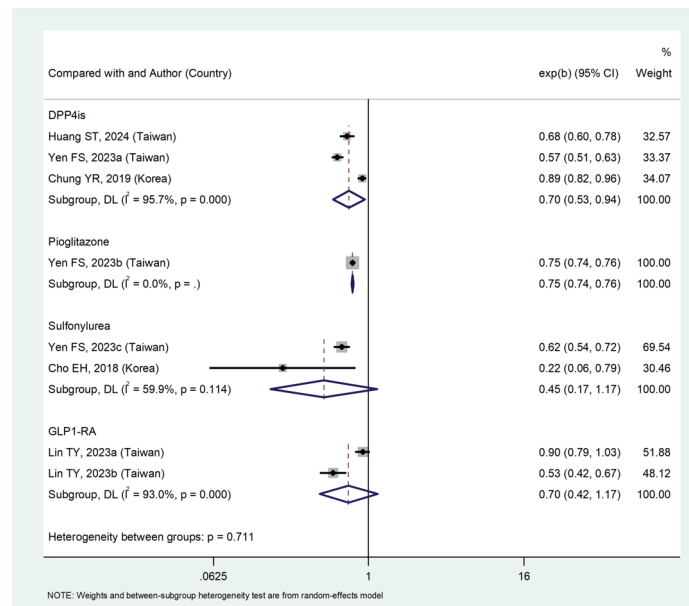
Figure 3. Evaluation of relationship between use of SGLT2 inhibitors and risk of diabetic retinopathy by compare group, with its 95% confidence interval.
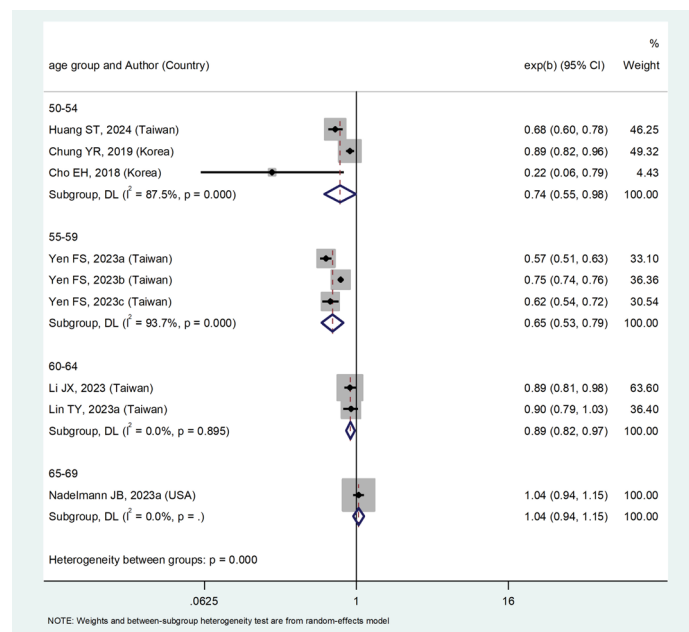

Figure 4. Evaluation of relationship between use of SGLT2 inhibitors and risk of diabetic retinopathy by age group, with its 95% confidence interval.

Discussion

SGLT2 inhibitors demonstrated a capability to diminish the incidence of diabetic retinopathy by as much as 23 percent, with males and individuals younger than 65 years emerging as the optimal demographic for these drugs' application. In a comparative evaluation of anti-diabetic medications, SGLT2 inhibitors outperformed pioglitazone and DPP4 inhibitors. Another study previously suggested that SGLT2 inhibitors may carry a reduced diabetic retinopathy risk in comparison to DPP4 inhibitors (24).

A meta-analysis by Li and colleagues aimed at evaluating the effect of SGLT-2 inhibitors on total ocular events and retinopathy in type 2 diabetes patients found no significant statistical correlation between the utilization of SGLT-2 inhibitors and the overall ocular events risk (RR: 0.97, 95% CI: 0.85, 1.11) or retinopathy (RR: 0.98, 95% CI: 0.84, 1.16) (26). Another meta-analysis on ocular disorders by Ma et al concluded that the occurrence of diabetic retinopathy did not notably differ between users of SGLT2i and the control group (OR: 0.80, 95%CI: 0.61, 1.06) (27). Tan and colleagues in their study indicated that the utilization of GLP-1 RA (RR: 0.98, 95%CI: 0.89,
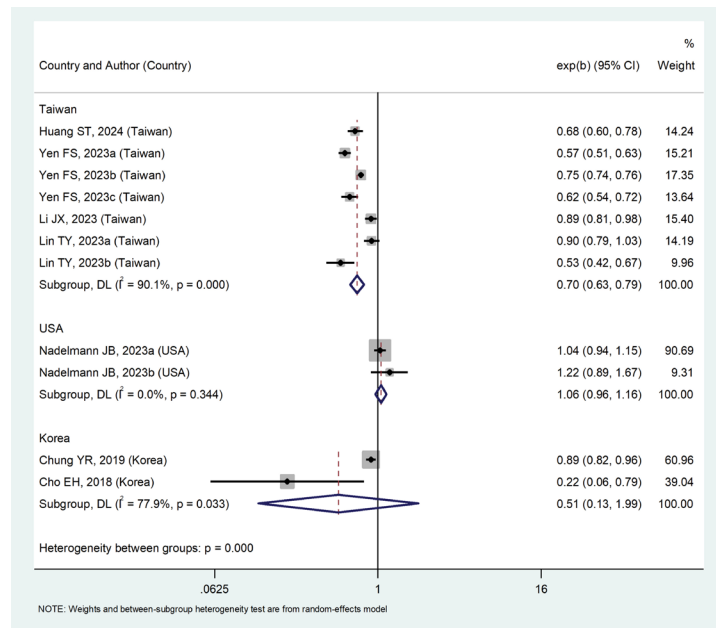
Figure 5. Evaluation of relationship between use of SGLT2 inhibitors and risk of diabetic retinopathy by countries, with its 95% confidence interval.
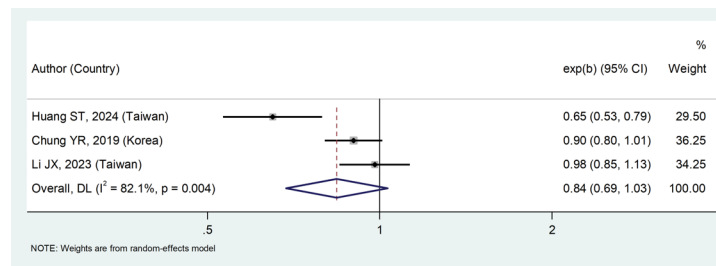

Figure 6. Evaluation of relationship between use of SGLT2 inhibitors and risk of diabetic retinopathy in women with its 95% confidence interval.
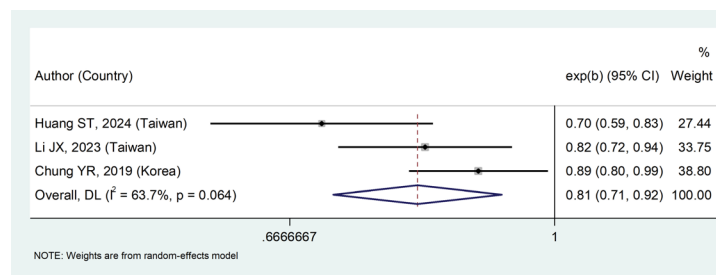

Figure 7. Evaluation of relationship between use of SGLT2 inhibitors and risk of diabetic retinopathy in men with its 95% confidence interval.

1.08), SGLT-2i (RR: 1, 95%CI: 0.79, 1.27), or DPP-4i (RR: 1.17, 95%CI: 0.99, 1.39) in type 2 diabetes patients, in comparison to placebo or other anti-diabetic drugs, did not significantly impact the diabetic retinopathy risk (28). These studies' final results must be consistent with our research's conclusive findings.

According to the findings of Zhou et al, the general administration of SGLT-2 inhibitors in patients with type 2 diabetes did not correlate with the onset of glaucoma, cataracts, retinal disease, or vitreous disorders in comparison to a control group. However, empagliflozin reduced the diabetic retinopathy risk compared to the control group (RR: 0.44, 95% CI: 0.20, 0.99) (29). This outcome is consistent with our study, and both indicate the predictive effects of SGLT-2 inhibitors on diabetic retinopathy.

In a meta-analysis by Igweokpala et al, the relationship between incretin-based drug use and diabetic retinopathy in patients with type 2 diabetes was investigated. The study concluded that there was no significant statistical
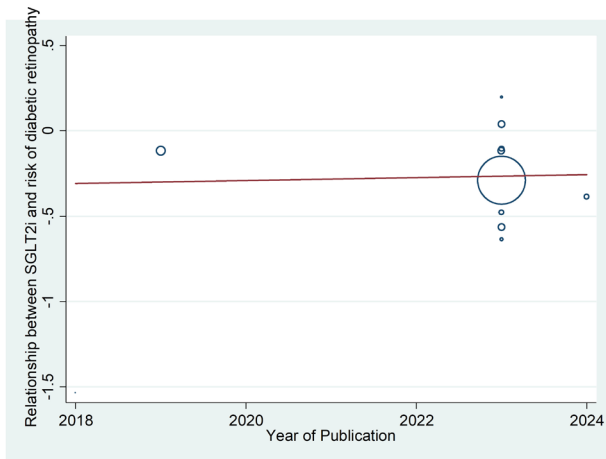
Figure 8. Meta-regression to investigate the relationship between "use of SGLT2 inhibitors and risk of diabetic retinopathy" and the year of publication of studies.

Figure 9. Meta-regression to investigate the relationship between "use of SGLT2 inhibitors and risk of diabetic retinopathy" and the year of publication of studies.
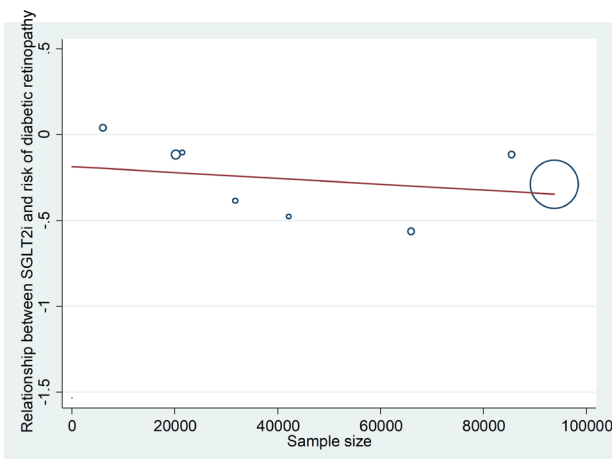
association between the utilization of DPP-4 inhibitors (RR: 0.98, 95% CI: 0.83, 1.17) or GLP-1 RAs (RR: 0.87, 95% CI: 0.56, 1.34) and the diabetic retinopathy risk (30). Another meta-analysis by Jiao et al found that treatment with GLP-1 RA did not increase the diabetic retinopathy risk in all the trials reviewed (OR: 1.17, 95% CI: 0.98, 1.39) (31). Furthermore, a network meta-analysis by Tang et al on patients with type 2 diabetes showed that DPP-4 inhibitors (OR: 1.20, 95% CI: 0.87, 1.65), GLP-1 RAs (OR: 1.19, 95% CI: 0.94, 1.52), and SGLT2 inhibitors (OR: 0.79, 95% CI, 0.49, 1.28) did not have a significant association with the diabetic retinopathy risk compared to placebo (32). These studies indicated no significant statistical correlation between the utilization of DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors and the diabetic retinopathy risk, which does not align with our study.

Conversely, Kapoor et al investigated the impact of using GLP-1 RA on diabetic retinopathy in a meta-
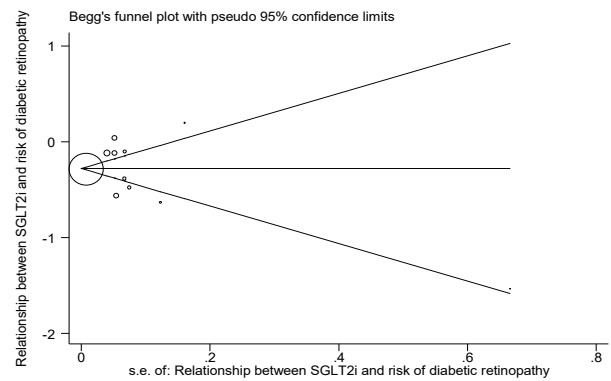

Figure 10. Publication bias plot.

analysis. They reported that the utilization of GLP-1 RA was associated with an increased early-stage diabetic retinopathy risk (RR: 1.31, 95% CI: 1.01, 1.68) and early-stage retinal side effects (RR: 1.29, 95% CI: 1.01, 1.66) in comparison to placebo (33).

Limitations of the study
The specific types of SGLT2 inhibitors utilized in the studies needed to be clarified. The duration and dosage of SGLT2 inhibitor usage varied across different studies. The geographic distribution of the studies was not uniform across various regions. The comparator drugs used in the control groups of the studies differed.

Conclusion
Overall, the administration of SGLT2 inhibitors, compared to control groups, resulted in a 23 percent reduction in diabetic retinopathy risk. Conversely, the administration of SGLT2 inhibitors did not affect the incidence of diabetic retinopathy in women, but it was associated with a 19 percent reduction in risk for men. Furthermore, the utilization of SGLT2 inhibitors decreased the diabetic retinopathy risk by 30 percent in comparison to DPP4 inhibitors and by 25 percent compared to pioglitazone. Additionally, SGLT2 inhibitors in the age groups of 50 to 54 years led to a 26 percent reduction, 55 to 59 years to a 35 percent reduction, and 60 to 64 years to an 11 percent reduction in diabetic retinopathy risk. However, this was different for the age group above 65 years. Hence, prescribing SGLT2 inhibitors to male diabetic patients under 65 years of age is a safe and effective option, especially when compared to pioglitazone and DPP4 inhibitors. SGLT2 inhibitors help control blood sugar levels and notably prevent the onset of diabetic retinopathy.

Authors' contribution

Conceptualization: Mobin Mohammadtabar and Shahrzad Ghaffariyan.
Data curation: Alireza Baghaei and Mobin Mohammadtabar.
Formal analysis: Farangis Yazdanjou and Farzin Banei.
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Methodology: Farzin Banei.
Project management: Mobin Mohammadtabar.
Resources: All authors.
Supervision: Shahriar Barkhordari.
Validation: Mohammad Shirvani and Mohammad Akbari.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical issues

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 with (ID: CRD42024523959) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1808). Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the author.

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