Systematic Review and Meta-Analysis

Medicine

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Long-term effect of sodium–glucose cotransporter 2 inhibitors in kidney functions

A systematic review and meta-analysis

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Abstract

Background: Sodium–glucose cotransporter 2 (SGLT2) inhibitors (such as dapagliflozin, empagliflozin, and canagliflozin) are essential for the treatment of type 2 diabetes because they improve the urine excretion of glucose. Although there are advantages, including weight loss and enhanced heart health, caution is necessary because of possible negative effects, such as higher urine output and euglycemic diabetic ketoacidosis. They may slow chronic kidney disease progression, therefore, renal function must be monitored. This study aims to determine the efficacy of SGLT2 inhibitors in the prevention of renal deterioration in terms of reduction of estimated glomerular filtration rate (eGFR) in patients with compromised renal functions.

Methods: This study aimed to document the long-term effects of SGLT2 inhibitors on kidney function. PubMed and Google Scholar were the key sources of scholarly publications, and Boolean operators were used to perform exact searches. Nine articles were considered relevant out of a total of 244, following extensive screening of titles, abstracts, and full texts according to PRISMA recommendations.

Results: This study included randomized, double-blind, placebo-controlled trials evaluating the long-term effects of SGLT2 inhibitors on renal function across patient demographics and locations. Clinical investigations showed different effects on eGFR across control and study groups, suggesting renal protection. A meta-analysis showed that SGLT2 inhibitors enhanced kidney function more than the controls.

Conclusion: This meta-analysis concluded that SGLT2 inhibitors have the potential to prevent eGFR reduction and improve renal function in patients with compromised renal function and underlying conditions such as chronic kidney disease or type 1 and 2 diabetes. However, this meta-analysis showed beneficial results in the prevention of renal deterioration within several follow-up periods, with an average of 11 to 12 months.

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, SGLT2 = sodium–glucose cotransporter 2, SMD = standardized mean differences.

Keywords: chronic kidney disease, compromised renal function, eGFR reduction, kidney function, long-term effects, meta-analysis, renal deterioration, SGLT2 inhibitors, systematic review, type 2 diabetes

1. Introduction

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel family of pharmaceuticals used in the treatment of T2DM. These medications promote greater expulsion of sugar in urine by blocking the kidneys' ability to reabsorb glucose. Recent findings highlight their many advantages over glycemic management, including positive effects on metabolic parameters, weight loss, and heart and nephron health. It appears that SGLT2 inhibitors decrease arterial pressure, muscle mass, and glycated hemoglobin concentrations, and they have been shown to enhance heart health in patients with elevated risk. However, in addition to their beneficial effects, these medications may have negative effects such as increased urination, a lack of water, and the possibility of euglycemic diabetic ketoacidosis. Thus, even if SGLT2 inhibitors show promise, their clinical usage requires a careful consideration of both the dangers and advantages of the treatment.[1–4]

SGLT2 inhibitors function by preventing the kidneys' SGLT2 from being active. This results in a decrease in the uptake of glucose, which increases the removal of sugar via urination and

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval was not necessary in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. The protocol was not registered.

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lowers glucose in the blood levels. Because of this unique mechanism, which functions independently of insulin, these inhibitors are effective for people with varying degrees of β-cell activity and insulin sensitivity. Moreover, in addition to their main function in controlling blood sugar levels, SGLT2 inhibitors have side effects that include lowering blood pressure, reducing body weight, and improving outcomes related to kidney and heart function.[5,6]

Canagliflozin, dapagliflozin, and empagliflozin are SGLT2 inhibitors that are commonly used. They act as a pharmaceutical armament against diabetes type 2 by controlling elevated glucose levels through improved urine glucose excretion. These well-known drugs have the extra advantage of having a low risk of hypoglycemia while lowering the heart rate, body mass index, and glycated hemoglobin levels. Empagliflozin is particularly noteworthy for its notable effects on cardiovascular outcomes.[7] It has been shown to significantly reduce mortality from cardiovascular disease and other causes as well as hospitalizations for cardiac failure in patients with preexisting cardiovascular conditions. Even if instances linked to volume depletion are uncommon, it is crucial to recognize possible side effects such as vaginal mycotic illnesses and infections of the urinary system.[7,8]

The kidneys play a crucial part in maintaining the equilibrium of glucose through a variety of precisely calibrated processes, which are essential to the complex of glucose regulation. These essential organs perform glucose production, absorbance of glucose, and reabsorption inside the proximal tubules, thereby functioning as a producer as well as a consumer of glucose and delicately regulating blood sugar levels. Interestingly, the kidneys efficiently filter out around half of the circulating insulin, acting as the main gatekeepers for insulin elimination.[9] Moreover, their crucial role in the reabsorption of glucose through sodium–glucose cotransporters emphasizes how important they are, especially when considering diabetes. Without question, the kidneys play a crucial role in maintaining the delicate balance of glucose homeostasis in the body.[10,11]

Reduced kidney function is a serious risk, increasing susceptibility to cardiovascular events, development of end-stage renal disease, and increased risk of death overall. A slight reduction in renal function, of between twenty and thirty percent, signals a significant increase in risk and calls for close observation and prompt action.[12] A major predictor for heart disease and stroke is impaired kidney function, which has detrimental effects on metabolic processes, dietary, and circulatory parameters. This risk is especially high in the elderly.[13] Beyond the physiological sphere, poor kidney function looms large over health-related aspects of life, increasing the risk of cardiovascular complications and mortality and causing both mental and physical wellness to diminish.[14]

Investigating the long-term effects of SGLT2 inhibitors on kidney function is of utmost importance, considering their capacity to slow the progression of chronic kidney disease (CKD) in patients with type 2 diabetes. These inhibitors have drawn notice due to their correlation with lower incidence rates of acute renal failure, composite renal outcomes, and albuminuria progression in individuals with type 2 diabetes.[15,16] Furthermore, their capacity to mitigate the yearly decrease in estimated glomerular filtration rate (eGFR) and urinary protein excretion in patients with CKD stages 3b–4 has highlighted their significant renoprotective benefits.[15] SGLT2 inhibitors, in particular, show promise in reducing the onset or aggravation of albuminuria, lowering intraglomerular pressure, and preventing hyperfiltration—all of which function as critical indicators of renal impairment. Therefore, a thorough analysis of the prolonged use of antagonists on renal function is essential to realizing their promise for preventing renal degradation and slowing the advancement of CKD in T2DM patients.[17,18]

This study aims to comprehensively evaluate the long-term efficacy of SGLT2 inhibitors, such as dapagliflozin, empagliflozin, and canagliflozin, in preventing renal deterioration among patients with compromised renal function. Specifically, the study seeks to investigate the reduction of eGFR as a marker of renal function decline in individuals receiving SGLT2 inhibitors. By conducting a systematic review and meta-analysis, the study aims to provide evidence-based insights into the potential renal protective effects of SGLT2 inhibitors and contribute to the optimization of treatment strategies for patients with conditions such as chronic kidney disease and type 2 diabetes. The advantage of this study lies in its comprehensive evaluation of the long-term effects of SGLT2 inhibitors on kidney function. By synthesizing evidence from multiple randomized, double-blind, placebo-controlled trials, the study provides a robust analysis of the renal outcomes associated with SGLT2 inhibitor therapy. The findings of this study can inform clinical practice by guiding healthcare professionals in the management of patients with compromised renal function, potentially leading to improved renal outcomes and patient care.

2. Method

2.1. Search strategy and research design

The study used online libraries like Google Scholar, PubMed, Elsevier, Bing Academic, and the Cochrane library, using MeSH terms like sodium–glucose transporter 2 inhibitors, kidney function, long-term effects, systematic review, meta-analysis, renal function, diabetes mellitus, sodium–glucose transporter 2, renal insufficiency, drug therapy.

The search methodology focused on finding reliable sources to collect information about the prolonged impact of SGLT2 inhibitors on renal functions compared to previous research. This study gathered pertinent clinical data relating to the topic by consulting reputable websites. PubMed and Google Scholar were the main resources for academic papers and articles. Using Boolean operators helped narrow down searches to find studies specifically studying the long-term effects of SGLT2 inhibitors on kidney function. Furthermore, the focus was locating articles highlighting different aspects of kidney function influenced by SGLT2 inhibitors. PRISMA analysis was used as a reference when selecting journals to make sure relevant research was included.[19] A systematic database search was performed to eliminate duplicate articles, identifying ten genuine journals for further investigation. The meta-analysis considered the number of patients in each group (study and control group) and eGFR at baseline and at follow-up, were considered to determine the change in eGFR. The study used the Cochrane collaboration tool for assessment of the risks of bias. Two reviewers independently (blinded to each other) evaluated all the studies for determination of the risks, which were based on 7 criteria (accuracy, reliability, relevance, clarity, completeness, validity, and timeliness).

Based on PRISMA guidelines,[19] an extensive search was conducted across several mentioned libraries yielding 244 studies. Study relevancy was assessed using titles and keywords, leaving 144 papers after deleting unmatched or repeated findings. We excluded 60 research owing to lack of relevance or different objectives after evaluating their abstracts. Further review of the discussion and conclusion parts narrowed the pool to 20 papers because 40 did not meet the study's objectives. After strict adherence to inclusion and exclusion criteria, a total of 9 studies were chosen to serve as references for the study. Figure 1 shows the study selection process in our meta-analysis.

2.2. Inclusion criteria

- Only randomized controlled trial and Clinical Trials were included.

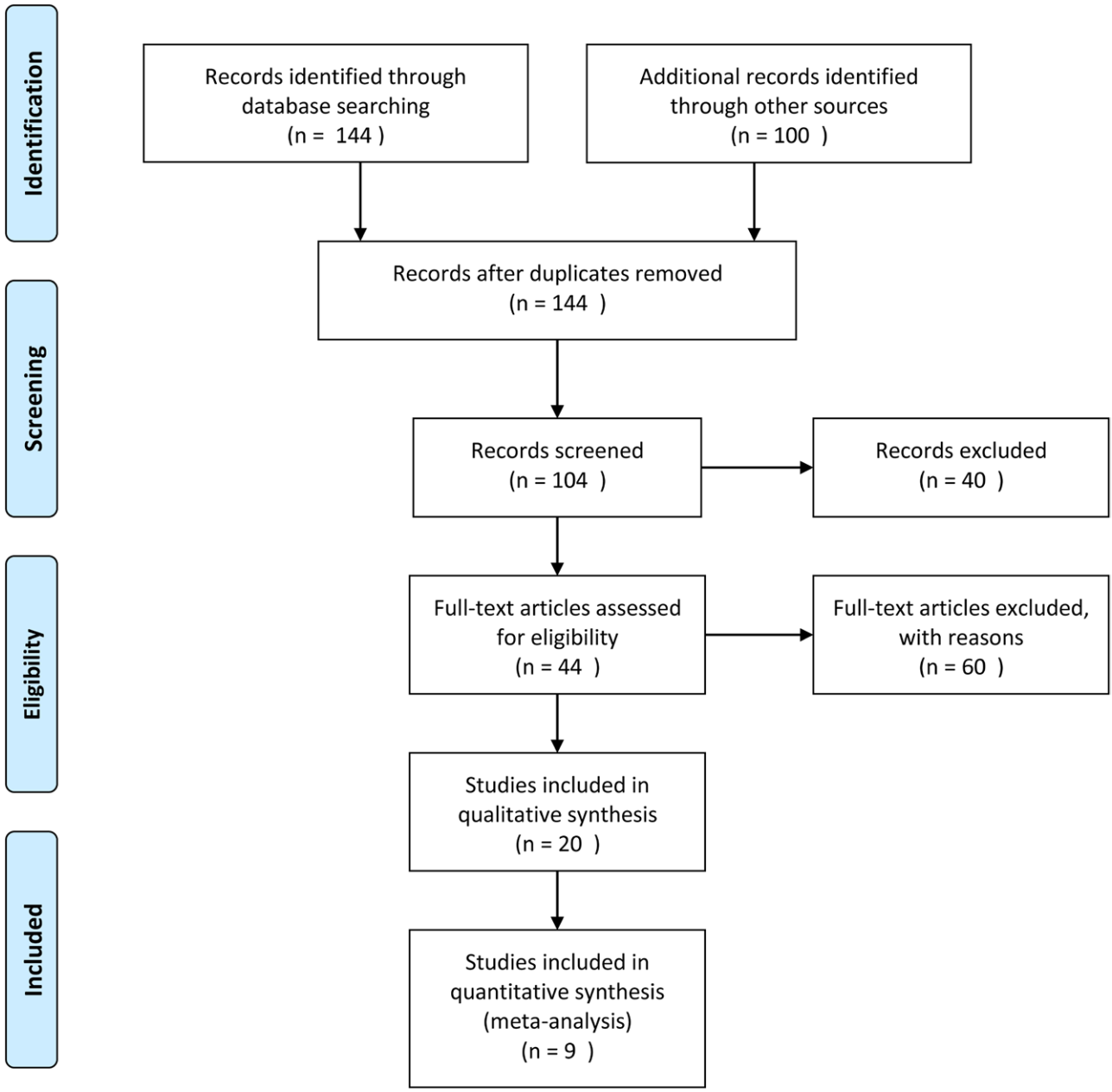

Figure 1. PRISMA flow chart.

- The studies which were conducted after 2015.
- The studies which investigated the change in eGFR.
- The studies that included drug interventions using SGLT2.

2.3. Exclusion criteria

- The studies that were not in English language.
- The studies which lacked consistent data or evidence.
- The studies which were not Open Access.

3. Results

This study included randomized, double-blind, placebo-controlled trials from different areas and patient demographics. Allegretti et al studied 10,142 type 2 diabetics at high risk of cardiovascular events in Sydney.[20] Chertow et al studied 4304 stage 4 chronic renal disease patients in the US.[21] Fioretto et al studied 321 type 2 diabetics with mild renal impairment in Spain.[22] Groop et al studied 251 type 1 diabetics in Finland.[23] Jhund et al studied 4743 UK patients with decreased ejection fraction heart failure.[24] Mosenzon et al studied 4742 Israeli type 2 diabetics with atherosclerotic cardiovascular disease or multiple risk factors.[25] Packer et al studied 3730 patients with class II–IV heart failure and ejection fraction < 40% throughout North America, Latin America, Europe, and Asia, including many with diabetes.[26] Perkovic et al studied 4401 US individuals with type 2 diabetes and albuminuric CKD.[27] Finally, van Raalte et al studied 1575 type 1 diabetics in the US and Canada.[28] These studies study the efficacy and safety of therapies in varied patient populations with distinct underlying diseases, advancing therapeutic management practices. Table 1 depicts the characteristics of the long-term effect of sodium–glucose cotransporter 2 inhibitors.

Clinical trials show variations in eGFR for control and study groups. Allegretti et al found a substantial improvement in eGFR in the study group after 24 weeks, while the control group

Table 1

Characteristics of the long-term effect of sodium–glucose cotransporter 2 inhibitors.

Study design	Study place	Study population	Number of included patients/participants	Underlying condition (heart disease, diabetes, absent/healthy)	Ref.
RCT	Sydney	Type 2 diabetes with high risk of cardiovascular events	10,142	Type 2 diabetes	Allegretti et al[20]
RCT	USA	Patients with stage 4 CKD	4304	CKD	Chertow et al[21]
RCT	Spain	Type 2 diabetes with moderate renal impairment	321	Type 2 diabetes	Fioretto et al[22]
RCT	Finland	Type 1 diabetes	251	Type 1 diabetes	Groop et al[23]
RCT	UK	Patients with HFrEF < 40%	4743	Chronic kidney disease	Jhund et al[24]
RCT	Israel	Type 2 diabetes with ASCVD or multiple risk factors for ASCVD	4742	Type 2 diabetes	Mosenzon et al[25]
RCT	North America, Latin America, Europe, Asia	Patients with class II–IV heart failure and ejection fraction < 40%	3730	diabetes	Packer et al[26]
RCT	USA	Type 2 diabetes with albuminuric CKD	4401	Diabetes	Perkovic et al[27]

ASCVD = atherosclerotic cardiovascular disease, CKD = chronic kidney disease, RCT = randomized controlled trial.

Table 2

List of changes in eGFR with follow-up period of patients.

Reference	Change in eGFR of control group (mL/min/1.73 m²)	Change in eGFR of study group (mL/min/1.73 m²)	Follow-up period
Allegretti AS et al (2019)[20]	–2.41	1.37	24 wk
Chertow GM (2021)[21]	–3.38	–2.15	28 d
Fioretto et al (2018)[25]	–12	–5	24 wk
Groop et al (2020)[24]	–4.7	–3.5	52 wk
Jhund et al (2021)[22]	–2.85	–1.09	Day 14–720
Mosenzon et al (2019)[23]	–2.85	–1.09	2 yr
Packer et al (2020)[26]	–3.17	–1.97	28 d
Perkovic et al (2019)[27]	–3.19 ± 0.15	–1.85 ± 0.13	2.62 yr
Raalte et al (2019)[29]	–2.8	–2.5	4 wk

eGFR = estimated glomerular filtration rate.

had a fall of -2.41 mL/min/1.73 m².[20] Chertow et al found a lower eGFR decline in the study group compared to the control group over 28 days (-2.15 vs -3.38 mL/min/1.73 m²).[21] Fioretto et al found a 24-week drop in eGFR for both groups, with the study group experiencing a smaller decrease (-5 vs -12 mL/min/1.73 m²).[22] Groop et al found a lesser decrease in eGFR in the study group compared to the control group during 52 weeks (-3.5 vs -4.7 mL/min/1.73 m²).[23] Jhund et al[24] and Mosenzon et al[25] found less eGFR reduction in the study groups after 720 days and 2 years, respectively. Packer et al observed a lesser eGFR drop in the study group compared to the control group after 28 days (-1.97 vs -3.17 mL/min/1.73 m²).[26] Perkovic et al found a reduced eGFR drop in the study group over 2.62 years compared to the control group (-1.85 vs -3.19 mL/min/1.73 m²).[27] van Raalte et al discovered a lesser eGFR decline in the study group compared to the control group over 4 weeks (-2.5 vs -2.8 mL/min/1.73 m²).[28] These data imply therapies may improve renal function throughout various follow-up periods (average follow-up period is 11 months), highlighting opportunities for long-term efficacy and safety research. Table 2 presents list of changes in eGFR with follow-up period of patients.

Figure 2 shows a forest plot of a meta-analysis that studied the effect of SGLT2 inhibitors on kidney function. Each row in the forest plot represents a different study. The studies are arrayed by their mean effect size, which is the difference in the change in kidney function between the SGLT2 inhibitor group and the control group. The effect size is measured in standardized mean differences (SMD). A positive SMD means that the SGLT2 inhibitor group had a greater improvement in kidney function than the control group. A negative SMD means that the SGLT2 inhibitor group had a smaller improvement in kidney function than the control group. The horizontal lines in each row represent the 95% confidence interval for that study's effect size. The wider the confidence interval, the less certain the result of that particular study. The diamond at the end of each horizontal line represents the point estimate of the effect size for that study. The bottom row of the forest plot shows the overall effect size across all of the studies. The overall effect size is -5.34, with a 95% confidence interval of -6.86 to -3.83. This means that, on average, patients who took SGLT2 inhibitors had a 5.34-point greater improvement in kidney function than those who did not take SGLT2 inhibitors.

The square at the bottom of the forest plot represents the overall confidence interval for the effect size. Since the confidence interval does not cross zero, we can be fairly certain that the effect of SGLT2 inhibitors is statistically significant.

There are some amounts of detection bias, selection bias and reporting bias. Otherwise, the included studies show that there is a low risk of bias. Figure 3 shows the summary of the risk of bias in the included studies.

Figure 4 presents data from various studies comparing changes in eGFR from baseline between study and control groups. The study group received SGLT2 inhibitors, which are drugs with the potential to prevent reductions in eGFR in patients with chronic kidney disease or conditions where GFR is estimated to be reduced. In the control group, which did not receive SGLT2 inhibitors, the changes in eGFR from baseline ranged from -12 to -2.41, with a total mean change of -5.16. Conversely, in the study group receiving SGLT2 inhibitors, the changes in eGFR from baseline ranged from -5 to 1.37, with a total mean change of -1.7175.

Overall, the data suggests that the study group receiving SGLT2 inhibitors experienced less decline in eGFR compared to the control group across the various studies, indicating the potential protective effect of these drugs in preventing reductions in kidney function.

4. Discussion

The positive long-term effects of SGLT2 inhibitors on kidney health in people with type 2 diabetes are highlighted by data from a comprehensive systematic review and meta-analysis conducted by Zhang et al that included 39 studies and 35 trials. All of the results together show a significant decline in the rate of acute renal failure or damage, composite renal outcomes, and the likelihood of the presence of albumin progression.[17] Also, Tsimihodimos et al[29] and Mirabelli et al[30] have shown that SGLT2 inhibitors are effective in reducing microalbuminuria, macroalbuminuria, and the worsening of nephropathy while also slowing down the reduction in eGFR. The significant renal

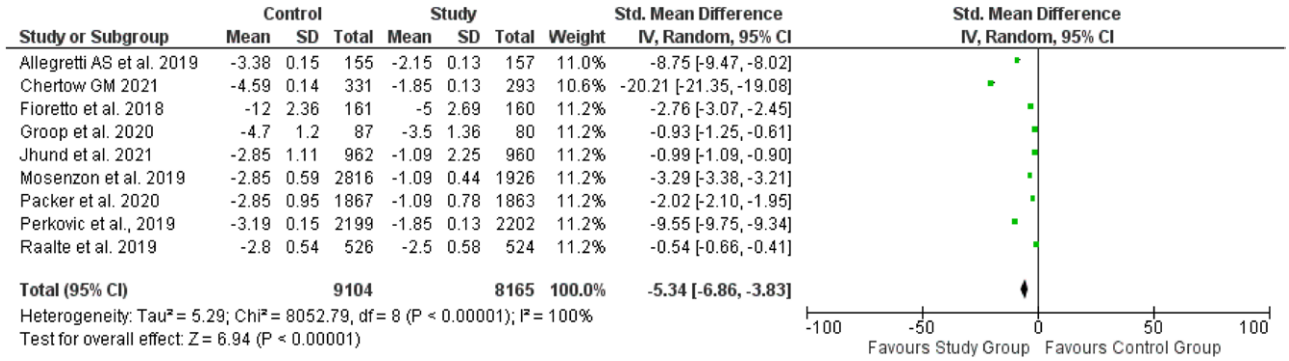

Figure 2. Forest plot showing the meta-analysis of the included studies.

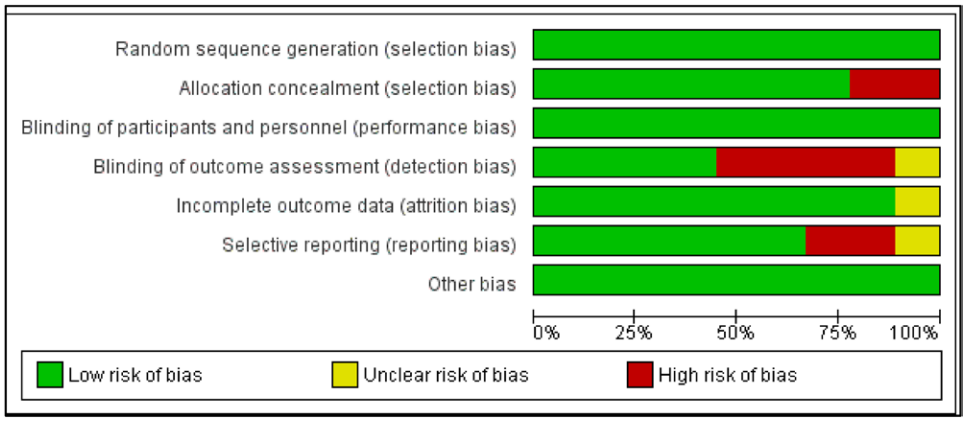

Figure 3. Summary of risk of biases of all the included studies.

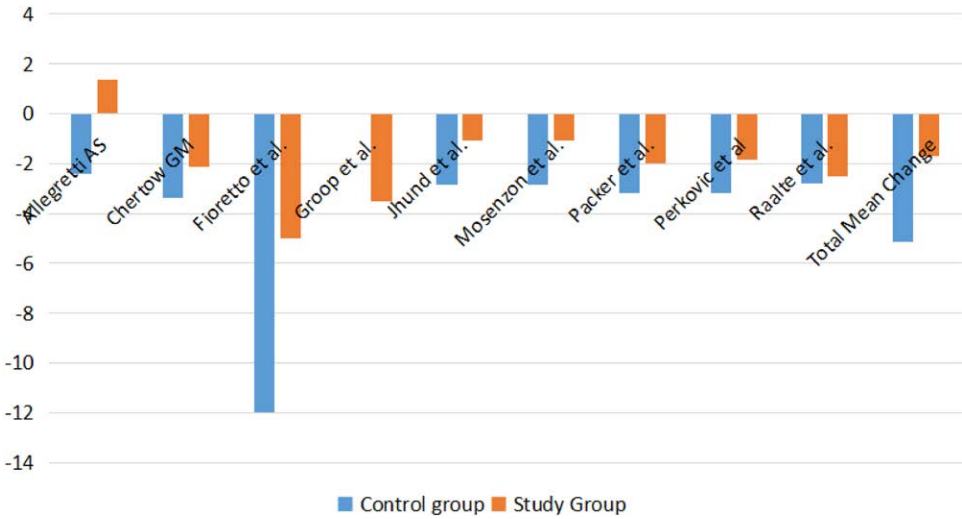

Figure 4. Change in eGFR in the study and control group of each included study and total mean change. eGFR = estimated glomerular filtration rate.

benefits provided by SGLT2 antagonists are demonstrated by this convincing data, highlighting their critical role in enhancing renal health results in long-term use in those battling diabetes of type 2.[17,29,30]

No discernible differences in the yearly decline slopes of eGFR were found between canagliflozin, dapagliflozin, empagliflozin, and various other SGLT2 antagonists in a comparative research conducted by Suzuki et al.[31] Interestingly, though, the study by Chun et al found that people with higher baseline levels of urine albumin-to-creatinine ratio had a greater ability of SGLT2 inhibitors to lower urine albumin-to-creatinine ratio.[32] Moreover, individuals who manifested overt albuminuria had a lower chance of experiencing unfavorable kidney outcomes than individuals who did not.[32] Even though these results offer insightful information, more research is necessary to confirm these findings and clarify the underlying causes of the variations in renal outcomes amongst SGLT2 medicines.

There are several intricate renoprotective pathways linked to SGLT2 inhibitors. First off, regardless of the state of glucose control, these inhibitors have a substantial effect on renal hemodynamics and glucose homeostasis by reducing

glomerular filtering and intraglomerular pressure via increased natriuresis and modification of tubuloglomerular mechanisms of feedback. This effect is seen in both diabetes-related and nondiabetic kidney condition scenarios. Second, SGLT2 inhibitors have positive effects on tubular function and renal oxygenation.[33–35]

They enhance renal cortical levels of oxygen, reduce tubular transport stress, and improve renal oxygenation—all of which are closely related to maintaining renal function and preventing chronic kidney disease. Finally, these inhibitors exhibit anti-inflammatory effects and help to lessen renal fibrosis and inflammation, which delay the development of nephropathy. All together, these diverse acts highlight the wide range of renoprotective benefits that SGLT2 inhibitors provide, offering encouraging treatment and prophylactic options for kidney problems.[34,35]

New research highlights the ability of SGLT2 blockers to slow down the course of CKD in people with diabetes of the second type. Notably, these medicines show significant benefits for the heart and kidneys, even with slight improvements in glycemic management. These benefits are especially noticeable in individuals with stage 3 CKD, and their effects on renal protection go beyond diabetics. Results from Yau et al EMPA-KIDNEY trial point to a possible extension of SGLT2 inhibitor signs to include patients with CKD who do not have albuminuria.[36] This would reinforce the drugs' effectiveness in protecting renal function in a variety of patient populations, regardless of the presence of insulin resistance.[26]

As per the most recent clinical guidelines, patients with diabetes with type 2 and mild-to-moderate CKD who have albuminuria or an eGFR between > 30 and < 90 mL/min/1.73 m^2 should be prescribed SGLT2 inhibitors. It is worth noting, nonetheless, that their effectiveness might be reduced in people with mild CKD, and their use is not recommended for individuals with severe CKD. The pragmatic aspects of their prescription include the expectation of a sharp drop in eGFR at start-up and careful monitoring of volume status.[27] Beyond diabetic management, SGLT2 inhibitors offer renoprotective benefits that include lowering the risk of acute renal injury and kidney disease that is end-stage. Additionally, they may be able to stop the onset of CKD and slow down its course in those with diabetes of the type 2 variety who are at varying risk of kidney disease.[18]

Because they provide little risk of low blood sugar, SGLT2 inhibitors are effective therapeutic drugs that can lower arterial pressure, weight, and HbA1c concentrations. They also show a variety of advantages, including heart protection, renoprotection, and possible antitumor action.[33] Similar drops in HbA1c levels are seen in comparison studies with DPP4 inhibitors; however, SGLT2 inhibitors are superior in improving the body's weight, systolic pressure, and ALT numbers, even if they cause less noticeable drops in eGFR levels.[28] Interestingly, in individuals with insulin-dependent diabetes, SGLT2 inhibitors have a better safety profile than SGLT1/2 drugs, with decreased risks of heart attack and stroke.[29]

Our study recognizes the limits of its methodology and emphasizes the need for additional long-term studies and actual-world proof to support its conclusions. The goal of future research should be to determine the best ways to dose and treat SGLT2 inhibitors in order to achieve the greatest effectiveness of therapy and minimize side effects.

5. Limitation of the study

In considering the interpretation of the findings, it has many limitations. First, the follow-up periods across trials were fairly short 11 to 12 months on average—thus really limiting the ability to question long-term efficacy and safety of SGLT2 inhibitors—their effect on renal function. Second, there was considerable heterogeneity among the studies due to differences in people enrolled and underlying conditions, but also study designs, all of which have an influence on outcomes and generalize the results over an entire population. Furthermore, the meta-analyses were dependent solely on previously published data, which might introduce bias since some of the studies did not report renal outcomes. Non-English language or non-open-access studies all exclude considerable evidence. The focus of this study is mainly on eGFR alone, implying that most vital clinical parameters indicating kidney health are overlooked or ignored by this approach. These are thus critical limitations that highlight the need for continued long-term realistic studies to verify these results.

6. Conclusion

This study concluded that SGLT2 inhibitors includes dapagliflozin and empagliflozin which have demonstrated significant benefits that slowing eGFR decline. In addition, it can improve kidney function in patients with diabetes or CKD. This systematic review and meta-analysis provide strong evidence which support their uses as a protective therapy for renal health. In addition, it also compared to control groups patients receiving SGLT2 inhibitors experienced smaller eGFR declines or even improvements. Even, it also highlighted the potential of these medications in preventing kidney deterioration. On the other hand, the Follow-up periods averaging from 11 to 12 months confirmed these advantages across various patient populations. The inhibitors also reduce albuminuria, intraglomerular pressure, and inflammation that contributing to long-term kidney health. Again, their effects in early-stage CKD are promising, they are most effective in moderate-to-advanced stages. This research emphasizes the significance of SGLT2 inhibitors as a therapeutic option which can protect renal function as well as improve outcomes in diabetes and CKD management. Further research is required to investigate extended benefits and refine treatment protocols.

Author contributions

Conceptualization: Yanqun Zheng.
Data curation: Jia Sun.
Methodology: Yanqun Zheng.
Software: Jia Sun.
Supervision: Yanqun Zheng.
Validation: Jia Sun.
Writing – original draft: Jia Sun.
Writing – review & editing: Yanqun Zheng.

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