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DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *The increase in type 2 diabetes has positioned it as the leading cause of chronic kidney disease (CKD) and is responsible for approximately half of all cases of end-stage kidney disease (ESKD) worldwide. Managing CKD in diabetic patients entails addressing its complications and minimizing the risk of other associated conditions, such as cardiovascular disease. This study aims to serve a comprehensive systematic review on diabetes management in CKD patients in literatures of the last 10 years.*

Methods: *The systematic review followed PRISMA 2020 standards and examined full-text English literature published between 2014 and 2024. This review excluded editorials, review papers from the same journal, and submissions without a DOI. Literature was sourced from online platforms such as PubMed, SagePub, SpringerLink, and Google Scholar.*

Result: *A total of 43,740 articles were retrieved from online databases (PubMed, SagePub, SpringerLink and Google Scholar). After three rounds of screening, four articles directly relevant to the systematic review were selected for full-text reading and analysis.*

Conclusion: *Chronic kidney disease (CKD) is a common and serious complication in individuals with diabetes. Management involves controlling hypertension and hyperglycemia, along with using ACE inhibitors like finerenone and SGLT2 inhibitors such as dapagliflozin, sotagliflozin, and bexagliflozin.*

Keyword: *CKD, treatment, diabetes mellitus*

INTRODUCTION

Chronic kidney disease (CKD) is a prevalent, serious, and costly complication among individuals with diabetes. The global population living with diabetes was estimated at 537 million in 2021, projected to reach 784 million by 2045. Over a quarter of these individuals suffer from CKD, with nearly 40% expected to develop the condition during their lifetime. The rise in diabetes prevalence has led to an increase in diabetes-related CKD cases. Diabetes is the leading cause of kidney failure worldwide, accounting for half of all new kidney failure cases in the U.S. and significantly raising the risk of cardiovascular diseases and mortality among those affected.[1]

The rise in type 2 diabetes has made it the primary cause of CKD and is behind roughly half of all end-stage kidney disease (ESKD) cases globally. In the United States alone, over 726,000 patients were living with ESKD in 2016, with between 66% and 86% of these cases linked to diabetes, varying by age and racial/ethnic backgrounds. Studies have shown that CKD is more prevalent in patients with type 2 diabetes who are over 65 years old compared to younger patients (58% vs 25%), and it is more common in African Americans than in non-Latino whites (43% vs 38%). The prevalence of diabetes is higher in those with ESKD than in the earlier stages of CKD. This is because diabetes can occur alongside other causes of CKD or emerge after the development of ESKD, especially in those who have received kidney transplants.[2]

In many cases, CKD does not manifest through noticeable symptoms, especially in its early stages, which makes routine screenings crucial for early detection. Healthcare guidelines, such as those from the American Diabetes Association (ADA) and the Kidney Disease: Improving Global Outcomes (KDIGO), strongly recommend that individuals with diabetes undergo annual screenings for CKD. This is particularly important since diabetes is a leading risk factor for the development of CKD.[1]

The guidelines specify that screening should begin immediately upon diagnosis for individuals with type 2 diabetes (T2D) because there is a high likelihood that signs of CKD might already be present at this stage. For individuals with type 1 diabetes (T1D), the recommendation is to start CKD screenings five years after their diabetes diagnosis since the onset of CKD is less common in the initial years following a T1D diagnosis.[1,3]

Despite these clear guidelines, the implementation of CKD screenings, especially for albuminuria—a key indicator of kidney damage—is not as widespread as it should be. This underutilization of recommended screenings can lead to delayed detection of CKD, which, in turn, limits the opportunities for early intervention and management of the disease. Early detection and treatment are critical for slowing the progression of CKD, managing its complications, and reducing the risk of other related conditions, such as cardiovascular disease.[3] This study aims to serve a comprehensive systematic review on diabetes management in CKD patients in literatures of the last 10 years.

METHODS

Protocol

The author carefully followed the rules laid out in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. This was done to make sure the study met all its standards. The selection of this methodological approach was specifically aimed at ensuring the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review examined the management of diabetes in CKD patients in literature over the past decade. This study meticulously analyzed data on literatures to provide insights and enhance patient treatment strategies. The primary objective of this paper is to highlight the collective significance of the identified key points.

Inclusion criteria for this study entail: 1) Papers must be in English, and 2) Papers must have been published between 2014 and 2024. Exclusion criteria comprise: 1) Editorials; 2) Submissions without a DOI; 3) Previously published review articles; and 4) Duplicate entries in journals.

Search Strategy

The keywords used for this research are “CKD”, “treatment”, and “diabetes mellitus”. The Boolean MeSH keywords inputted on databases for this research are: *"CKD"[All Fields] AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields])*

Data retrieval

The authors assessed the studies by reviewing their abstracts and titles to determine their eligibility, selecting relevant ones based on their adherence to the inclusion criteria, which aligned with the article's objectives. A consistent trend

observed across multiple studies led to a conclusive result. The chosen submissions had to meet the eligibility criteria of being in English and a full-text.

This systematic review exclusively incorporated literature that met all predefined inclusion criteria and directly pertained to the investigated topic. Studies failing to meet these criteria were systematically excluded, and their findings were not considered. Subsequent analysis examined various details uncovered during the research process, including titles, authors, publication dates, locations, study methodologies, and parameters.

Quality Assessment and Data Synthesis

Each author independently evaluated the research presented in the title and abstract of the publication to determine which ones merited further exploration. The subsequent stage involved assessing all articles that met the predefined criteria for inclusion in the review. Decisions on including articles in the review were based on the findings uncovered during this evaluation process. This criterion aimed to streamline the paper selection process for further assessment, facilitating a comprehensive discussion of previous investigations and the factors that made them suitable for inclusion in the review.

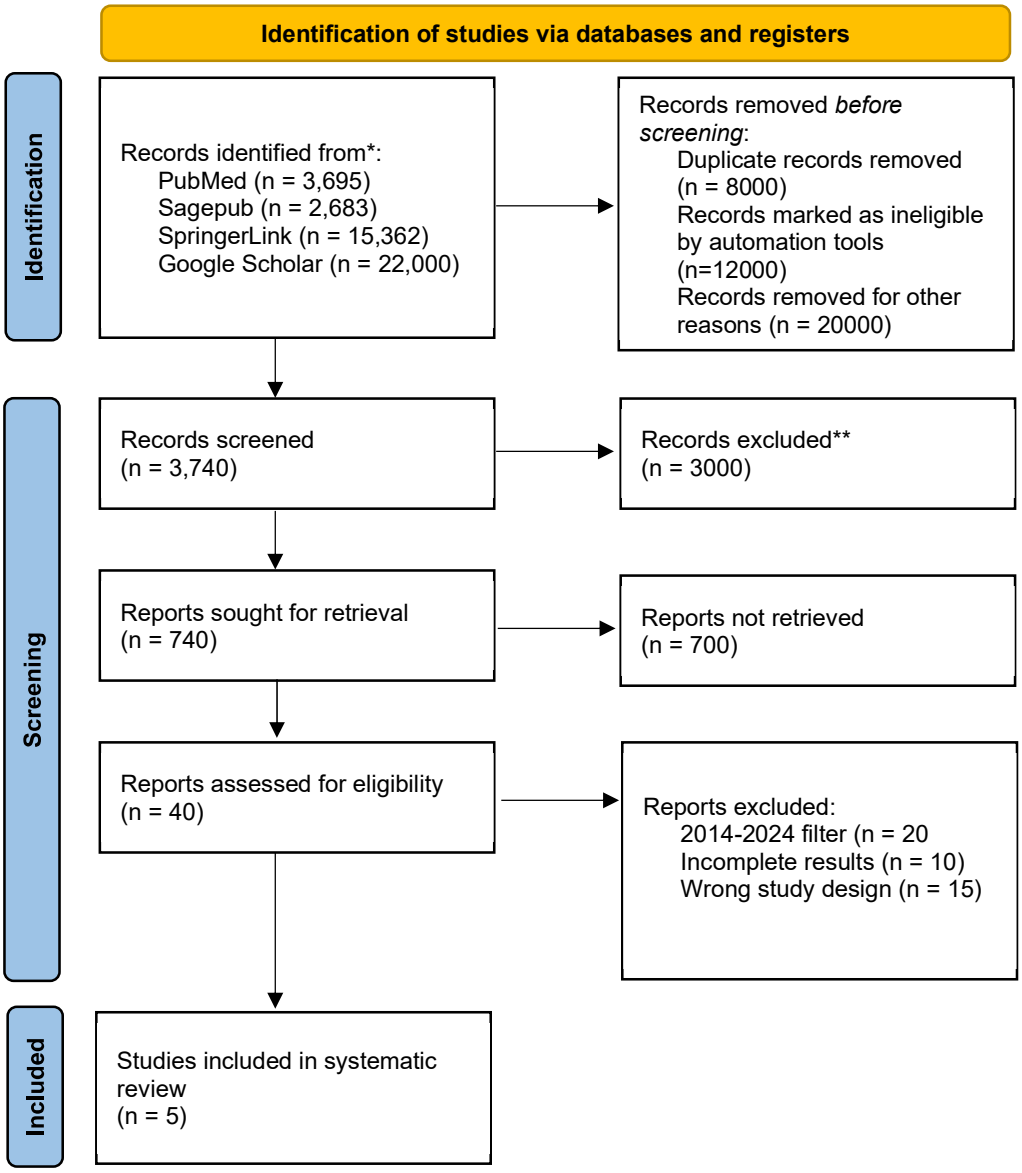

Figure 1. Article search flowchart

RESULT

The initial number of articles retrieved from online databases (PubMed, SagePub, SpringerLink, and Google Scholar) is 43,740 articles. After conducting three levels of screening, five articles that directly relate to the current systematic review

have been chosen for further assessment through full-text reading and analysis. Table 1 presents the selected literature included in this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Bakris, et al.[4] (2020)	USA	Randomized controlled trial	5734 patients with CKD and DM2	In a double-blind trial, 5734 CKD patients with type 2 diabetes were randomly assigned to receive either finerenone or a placebo. Finerenone showed a reduction in kidney failure, significant eGFR decrease, or death from renal causes by 18% compared to placebo. Additionally, finerenone demonstrated a slight decrease in major cardiovascular events. However, the finerenone group had a higher rate of hyperkalemia-related trial discontinuation compared to placebo.
Heerspink, et al.[5] (2020)	Groningen, Netherlands	Randomized controlled trial	4304 patients	In a trial involving 4304 participants with impaired kidney function, dapagliflozin significantly reduced the risk of kidney disease progression or death from renal or cardiovascular causes compared to placebo. The trial was stopped early due to the notable effectiveness of dapagliflozin, which showed a 39% reduction in primary outcome events over a median follow-up of 2.4 years. Importantly, dapagliflozin's safety profile remained consistent throughout the trial, and its benefits were observed across various subgroups, including individuals with and without type 2 diabetes.
Škrtić, et al.[6] (2021)	Canada	Retrospective study		Five male patients with type 2 diabetes (T2D) and a history of

				hypertension who underwent nephrectomy due to renal cell carcinoma were identified. They initiated SGLT2 inhibitor therapy post-nephrectomy, with no concurrent diuretic use and all receiving renin-angiotensin system (RAS) inhibition therapies. The time from nephrectomy to SGLT2 inhibitor initiation varied from 5 to 74 months. Baseline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) values were recorded, with mean values of 49 mL/min/1.73 m^2 and 8.7 mg/mmol, respectively. After 6 months of SGLT2 inhibition, mean eGFR and ACR values increased to 58 mL/min/1.73 m^2 and 23.8 mg/mmol, respectively. After 16 to 18 months of follow-up, mean eGFR and ACR values were similar to baseline. Systolic blood pressure remained stable throughout the study period. No adverse events related to acute kidney injury (AKI), electrolyte disturbances, ketoacidosis, or genitourinary infections were reported during the 18-month follow-up. The study suggests that SGLT2 inhibition may be beneficial for kidney protection in patients post-nephrectomy, but larger prospective studies are needed to confirm its efficacy and safety in this population.
Bhatt, et al.[7] (2021)	Boston, USA	Randomized controlled trial	10,584 patients	Out of 19,188 screened patients, 10,584 were enrolled, with 5292 assigned to the

				sotagliflozin group and 5292 to the placebo group, followed for a median of 16 months. The sotagliflozin group showed a lower rate of primary endpoint events (5.6 events per 100 patient-years) compared to the placebo group (7.5 events per 100 patient-years), with a hazard ratio of 0.74 ($p<0.001$). Rates of deaths from cardiovascular causes were similar between the groups. Sotagliflozin demonstrated a reduction in the original coprimary endpoints of cardiovascular events and hospitalizations for heart failure. However, adverse events such as diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin.
Allegretti, et al.[8] (2019)	Multicenter	Randomized controlled trial	312 patients	In a study involving 312 patients from 54 sites, bexagliflozin was observed to significantly decrease hemoglobin A1c levels by 0.37% (with a 95% CI ranging from 0.20% to 0.54%; $p < 0.001$) compared to a placebo. Individuals with CKD stages 3a and 3b also experienced reductions in hemoglobin A1c levels by 0.31% ($p = 0.007$) and 0.43% ($p = 0.002$), respectively. Bexagliflozin additionally led to decreases in body weight (1.61 kg; $p < 0.001$), systolic blood pressure (3.8 mm Hg; $p = 0.02$), fasting plasma glucose level (0.76 mmol/L; $p = 0.003$), and albuminuria (with a geometric mean ratio

				reduction of 20.1%; p = 0.03). Adverse event rates were similar across treatment groups.

Bakris, et al.[4] (2020) assessed the role of finerone on CKD patients with DM2 by analyzing the incidence of kidney failure, a significant eGFR decrease, or death from renal causes, and a secondary composite outcome focusing on cardiovascular health. The results showed that finerenone showed a reduction in kidney failure, significant eGFR decrease, or death from renal causes by 18% compared to placebo. Additionally, finerenone demonstrated a slight decrease in major cardiovascular events. However, the finerenone group had a higher rate of hyperkalemia-related trial discontinuation compared to placebo.

Heerspink, et al.[5] (2020) showed that dapagliflozin significantly reduced the risk of a composite outcome including a sustained decline in estimated glomerular filtration rate (GFR), end-stage kidney disease, or death from renal or cardiovascular causes when compared to placebo.

Škrtić, et al.[6] (2021) suggested that SGLT2 inhibition may be beneficial for kidney protection in diabetic patients post-nephrectomy. No adverse events related to acute kidney injury (AKI), electrolyte disturbances, ketoacidosis, or genitourinary infections were reported during the 18-month follow-up.

Bhatt, et al.[7] (2021) showed that sotagliflozin reduced the risk of cardiovascular events and heart failure hospitalizations in patients with diabetes and chronic kidney disease but was associated with certain adverse effects.

Allegretti, et al.[8] (2019) demonstrated that bexagliflozin effectively reduces hemoglobin A1c levels in patients with diabetes and stage 3a/3b CKD, along with beneficial effects on weight loss, blood pressure reduction, and albuminuria, without an observable increase in adverse events.

DISCUSSION

Chronic kidney disease (CKD) is a prevalent, serious, and expensive complication among individuals with diabetes. The International Diabetes Federation predicts a significant rise in diabetes cases, estimating 537 million people living with diabetes in 2021, expected to increase to 784 million by 2045. CKD affects over 25% of people with diabetes, with approximately 40% developing CKD during their lifetime. As diabetes rates increase, so does the proportion of CKD cases attributed to diabetes.[1]

The interaction between the kidney, glucose, and insulin is complex. During feeding, the kidney removes up to 20% of circulating glucose, while during fasting, it can produce up to 25% of blood glucose through gluconeogenesis. The liver clears about 40% to 50% of endogenous insulin, with the rest entering the circulation. Insulin is filtered by the glomerulus (up to 60%-65%) and reabsorbed by proximal tubular cells, with additional insulin transported to these cells from postglomerular peritubular vessels. Around 1% of insulin is excreted in urine after degradation. Notably, the kidney metabolizes a larger portion, up to 80%, of exogenous insulin due to bypassing first-pass metabolism in the liver.[9]

In chronic kidney disease (CKD), glucose metabolism is influenced by various mechanisms. These include impaired glucose disposal by muscle and peripheral tissues due to uremia, reduced insulin removal by the damaged kidney, a persistent mild inflammatory state, and oversecretion of counterregulatory hormones.[2]

New therapies are required for managing cardiorenal diseases such as CKD and diabetes, with evidence supporting the role of overactivation of the mineralocorticoid receptor in their pathophysiology. This overactivation leads to inflammation and fibrosis, contributing to progressive kidney and cardiovascular dysfunction. International guidelines recommend controlling hypertension and hyperglycemia, along with using renin-angiotensin system (RAS) blockers (ACE inhibitors or ARBs) and, more recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors for managing CKD in patients with type 2 diabetes.[4]

In patients with both CKD and type 2 diabetes, those treated with finerenone showed a reduced risk of primary outcome events, including kidney failure, significant eGFR decline, or renal-related death, compared to those receiving a placebo. Additionally, the finerenone group experienced a lower risk of key secondary outcome events, such as cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure hospitalization. [4]

An elevated risk of heart failure and ischemic events is observed in patients with diabetes and chronic kidney disease. SGLT-2 inhibitors have proven effective in treating type 2 diabetes mellitus and lowering the risk of heart failure hospitalization, regardless of previous heart failure occurrence. Randomized trial evidence supports the utilization of

SGLT2 inhibitors in patients with chronic kidney disease, irrespective of their diabetes status. The kidney-protective effects of SGLT2 inhibitors were demonstrated in patients with type 2 diabetes and chronic kidney disease. Previous study showed that SGLT2 inhibitors extend their kidney-protective benefits to a broader population, including those without type 2 diabetes, who typically rely on ACE inhibitors as the only proven pharmacological treatment for kidney failure prevention.[5]

SGLT2 inhibition is increasingly recognized as a fundamental aspect of nephrology care, aimed at mitigating kidney function decline, cardiovascular risk, and mortality. Heerspink, et al.[5] (2020) showed that dapagliflozin significantly reduced the risk of a composite outcome including a sustained decline in estimated glomerular filtration rate (GFR), end-stage kidney disease, or death from renal or cardiovascular causes when compared to placebo. Bhatt, et al.[7] (2021) also demonstrated that sotagliflozin reduced the risk of cardiovascular events and heart failure hospitalizations in patients with diabetes and chronic kidney disease but was associated with certain adverse effects. Similarly, Allegretti, et al.[8] (2019) demonstrated that bexagliflozin effectively reduces hemoglobin A1c levels in patients with diabetes and stage 3a/3b CKD, along with beneficial effects on weight loss, blood pressure reduction, and albuminuria, without an observable increase in adverse events.[5,7,8]

Škrtić, et al.[6] (2021) also suggested that SGLT2 inhibition may be beneficial for kidney protection in diabetic patients post-nephrectomy. No adverse events related to acute kidney injury (AKI), electrolyte disturbances, ketoacidosis, or genitourinary infections were reported during the 18-month follow-up. These findings underscore the potential of SGLT2 inhibitors as an adjunct therapy, alongside ACE inhibitors or ARBs, for managing chronic kidney disease, regardless of diabetes status.[5–7]

CONCLUSION

Chronic kidney disease (CKD) is a prevalent, serious, and expensive complication among individuals with diabetes. The management of CKD in diabetic patients involves controlling hypertension and hyperglycemia, along with the use of ACE inhibitors such as finerone and sodium-glucose cotransporter 2 (SGLT2) inhibitors such as dapagliflozin, sotagliflozin, and bexagliflozin.

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