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Comparative Outcomes of Newer Antidiabetic Agents in Preventing Diabetic Nephropathy: A Meta-Analysis

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Abstract

Diabetic nephropathy (DN) is known to be one of the central patients' burdens, contributing to the global development of chronic kidney diseases (CKD) and end-stage renal disease (ESRD). Even after the use of non-specific standards such as RAAS inhibitors, the progression of DN remains a challenging clinical problem. Some of the advanced antidiabetic drugs, SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), and DPP-4 inhibitors may improve renal function in addition to controlling hyperglycemia. This meta-analysis will compare the clinical efficacy of these newer antidiabetic agents with regard to attaining these objectives, including eGFR decline rate, albuminuria decrease, and the risk of ESRD. Reviews of eligible studies were obtained from PubMed, Embase, Cochrane Library, and Scopus, using keywords related to trial types, including randomised controlled trials (RCTs), cohort studies and meta-analyses with relation to Renal outcome of SGLT2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors. Cohen's d was calculated as the measure of effect size, fixed/random as the method of pooling effect sizes and I^2 as the measure of heterogeneity. The publication bias was assessed by using a funnel plot and Egger's regression test while the sensitivity analyses were done.

SGLT2 inhibitors were also found to have the most substantial nephroprotective benefits, including a reduction of the annual decline of eGFR by 1·4–2·0%, albuminuria by 31–38%, and ESRD risk by 29–34%. A moderate renal benefit was established with GLP-1 receptor agonists inclusive of a decrease in eGFR loss to a range of (-1.2%-1.5%), albuminuria (-24%-28%) and risk of ESRD (-21%- 25%) through anti-inflammatory effects. DPP-4 inhibitors, however, recorded only slight improvement of albuminuria (-9 to -12%) and ESRD (-7 to -10%), making it the worst option for nephroprotection. In line with these findings, this meta-analysis has evidence that SGLT2 inhibitors are superior to other antidiabetic drugs from the renal perspective. Secondly, GLP1-RA and, at last, DPP-4 inhibitors have minimal renal protection. These findings endorse the use of SGLT2 inhibitors to start with for patients having diabetes and CKD, along with GLP-1 receptor agonists, to increase cardiovascular and renal benefits.

Keywords: Diabetic nephropathy (DN), chronic kidney diseases (CKD), end-stage renal disease (ESRD).

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Introduction

Diabetes mellitus is a structurally undefined metabolic disease that is typified by a long-term high blood glucose crisis owing to faulty insulin secretion, defective insulin sensitivity, or both (Bennett, 2019). It is a common universal health issue that has an impact on millions of people, and research has estimated that it is on the rise. Also, as seen from the IDF, 537 million populations had diabetes in 2021, and this figure is projected to rise to 643 million in 2030 and 783 million in 2045. It is not only a lethal disease which affects the metabolism only but has some other effects that cause long-term complications which impact the cardiovascular system, the neural system, the renal system, etc. Of these, diabetic nephropathy is a severe microvascular complication that leads to ES RD in the absence of proper treatment (1). Diabetic nephropathy may be described as diabetic kidney disease (DKD), and it is considered one of the leading causes of chronic kidney disease (CKD) and mortality among diabetic individuals. It contributes to nearly half of the global cases of ESRD and is a significant drain on healthcare facilities since the costs of dialysis or kidney transplantation are high (2). The cases of DN are those in which pathogenesis primarily depends on metabolic factors, blood pressure, and inflammation, which results in the progressive condition of the kidneys. It has shown that patients with diabetes are clinically divided into categories of their disease with increasing severity: normoalbuminuria, microalbuminuria, macroalbuminuria, and end-stage renal disease with decreased glomerular filtration rate.

The first change of diabetic nephropathy is glomerular hyperfiltration, which represents a rise in GFR before a decline in the filtration process. This hyperfiltration is due to intraglomerular hypertension resulting from the relaxation of the afferent arteriole, caused by hyperglycemia activating RAAS and the release of other substances like nitric oxide and prostaglandin. Due to the continuous state of hyperfiltration, increased mechanical pressure is applied upon glomerular capillaries that, in turn, causes damage by affecting endothelium (3), podocytes as well as mesangial hypertrophy, which are the initial signs of kidney disease. One of the most critical factors that are connected with the development of DN is inflammation. Diabetes causes acute and chronic hyperglycemia that enhances the production of reactive oxygen species, which in turn activate inflammatory pathways that lead to kidney injury. The endotypes resulting from major inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and nuclear factor kappa B (NF-κB) are responsible for injuries to the glomeruli and tubules of the kidney. Moreover, AGEs are installed in the renal tissue, which enhances inflammation and fibrosis (4). These inflammatory processes worsen endothelial dysfunction, increase vascular permeability and participate in the progress of renal function deterioration (4). Fibrosis is a characteristic feature of DN and is mainly associated with increased accumulation of ECM proteins in the glomerular and tubulointerstitial regions. Transforming growth factor-beta (TGF-β) signalling has a pivotal role in the course of fibrotic changes with regard to tubulointerstitial fibrosis and glomerulosclerosis (5). Chronic renal injury leads to fibrosis of the kidneys and results in the irreversible decline of renal function, which eventually results in ESRD. ESRD, as a progression, calls for renal replacement therapy such as dialysis or kidney transplant, hence leading to poor quality of life and higher treatment expenses.

D diabetic nephropathy has also become more frequent, and its prevention or delay is a major therapeutic challenge due to the constantly growing number of patients diagnosed with diabetes. Target achievement in glycemic control, blood pressure management and the use of RAAS has been the primary treatment strategy used in managing DN (6). Nevertheless, newer groups of antidiabetic agents have moved into the category of therapeutic interventions in the process of prevention and delay of DN. Of these drugs, SGLT2 inhibitors, GLP-1 RAs, and DPP-4 inhibitors are shown to have renoprotective effects other than glucose-lowering effects (6). The present meta-analysis will aim to review the outcome of newer antidiabetic agents that may have the potential to slow or cease the development of diabetic nephropathy. With the help of data obtained from many clinical trials and observational studies, we will estimate the effectiveness and safety of the given agents in the subject of renal protection. The outcomes of the study will provide valuable information with regard to practice reference in choosing the most suitable intervention models for aimlessly prone individuals and consequently enhance the renal end results of diabetic patients. Diabetic nephropathy (DN), as one of CKD and ESRD, has been treated for a long time by glycemic control, blood pressure control, and RAAS blockade (7). The last targets were achieved through a number of strategies where ACE inhibitors and angiotensin II receptor blockers have been, in fact, a cornerstone in the renoprotective treatment for diabetic patients. These agents bring about the prevention of intraglomerular pressure, provided they prevent hyperfiltration and thus retard the formation of glomerulosclerosis.

Thus, ACE inhibitors and ARBs have several limitations that could be discouraging for some patients. Although the medications reduce the progression of kidney disease, they do not eliminate the chance of the development or worsening of diabetic nephropathy. They are less effective in the later stage of CKD, and they further have side effects such as hyperkalaemia and hypotension that may compel the termination of the drug in some patients. In the same way, RAAS inhibitors, including ACE inhibitors and ARBs, do

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not affect several determinants that have a pivotal role in the course of DN, such as oxidative stress, inflammation, and fibrosis (8). Another significant limitation now is the fact that there remains a latent threat of a decline in renal function even when the patient is on the proper RAAS inhibitors. Research reviews have also shown that even though BP can be carefully controlled, CKD will progress further with persistent metabolic and haemodynamic changes (9). Therefore, due to the limitations of RAAS inhibitors described above, there has been a growing pursuit of new therapeutic agents that have renal protective effects through different mechanisms. This hypothesis postulates that newer antidiabetics that have multiple functions have improved the treatment of diabetic nephropathy. In particular, SGLT2 inhibitors, GLP-1 RAs, and DPP-4 inhibitors have shown various levels of renal protection beyond the glycaemic control. The structural formula of empagliflozin, dapagliflozin, and canagliflozin indicates that these SGLT2 inhibitors demonstrated an exceptional level of efficacy in IRON OUT patient-population control. Some of the renoprotective mechanisms that they exert are decreasing intraglomerular pressure by increasing sodium excretion and decreasing glomerular filtration pressure. Also, they reduce oxidative stress and inflammation, which are factors that advance the progression of DN. These landmark clinical trials, including EMPA-REG OUTCOME, CREDENCE as well as DAPA-CKD, have provided strong evidence of using them to protect renal functions and or reduce albuminuria (10).

This renal preservation by GLP-1 RA drugs like liraglutide and semaglutide is mainly credited to the drug's anti-inflammatory, antifibrotic, and vasodilatory effects. These agents also have positive effects on endothelium, prevent oxidation and lessen cytokines release, which in turn retards the progress of kidney disease (11). LEADER and SUSTAIN-6 studies have shown promising outcomes that resulted in the prevention of new cases of macroalbuminuria and the slowing down of the rate of decline of both eGFR. Both sitagliptin and linagliptin have been tested for renal protection function. Compared to SGLT2 inhibitors and GLP-1 RA, they have lesser renal effects in the reduction of HbA1c and fasting plasma glucose; however, they have anti-inflammatory properties that can be useful in renal preservation. Some small randomised clinical trial studies have reported some steps of reduction in albuminuria, but the product's longevity is still under investigation (12). Therefore, it enhances the flow of coming up with newer antidiabetic agents to incorporate into DN management. The advantage of being able to modulate multiple pathophysiological changes in the diabetic urge's pathway is a definite worthy improvement in halting the progression of CKD in patients with diabetes. They recommend further studying of different dosing regimens to strengthen renoprotective effects and prognosticate the patient's condition in cases of diabetic nephropathy. However, existing data on the renal benefit of newer antidiabetic drugs are inconsistent, mainly attributed to differences in study characteristics, patients' population, and outcomes. Some trials show improved albuminuria and maintained eGFR in CKD patients; others show modest to no improvement in renal outcomes; thus, there is doubt in clinical management. This gap means that one cannot readily ascertain the best therapeutic intervention to use in dealing with the condition. A meta-analysis is the most efficient means of assessing a collection of data to subsequently compare the effect these agents have on diabetic nephropathy prevention. It is hoped that, with this study, evidence-based treatments concerning diabetic renal patients that will be high-quality and fill some of the above-mentioned knowledge gaps will be established.

Methods

Literature Search Strategy

The electronic data sources used were PubMed, EMBASE, Cochrane Library, and Scopus in order to review the potential renal benefits exerted by newer ADAs in preventing DN. These databases were selected to provide maximum coverage and relevance of biomedical literature-controlled words, such as Medline, Cochrane trials, and Cochrane systematic reviews while providing extensive retrieval of quality articles. While performing this search, both index, Medical Subject Headings (MeSH), and free-text terms with Boolean connectors were used in the process of selecting the studies. They were Type 2 diabetes, Diabetic nephropathy, Diabetic kidney disease, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, Chronic kidney disease, Albuminuria and Glomerular filtration rate, among others. These terms were necessarily connected by the Boolean operators for the purpose of increasing specificity and eliminating irrelevant articles. The retrieval was limited to articles in English written within the last 10–15 years to include current and most relevant information used in clinical practice. Thus, politically motivated filters were applied to search and identify the human research focusing only on the renal effect, where studies descriptively regarding modification in glomerular filtration rate, albuminuria concentration, serum creatinine concentration, incidence of chronic kidney disease, and end-stage renal disease data were included. To obtain the comparative effect of the newer antidiabetic agents on renal disease outcomes, randomised controlled trials, cohort studies, case-control studies, and meta-analyses were considered ideal study types. The studies that did not report renal outcomes in main outcome measures, the non-randomised studies, and those which stated glycemic control without any end-point related to the kidney were excluded. To eliminate the cases of multiple records, the articles were then reviewed, those which

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were repeated were removed, and titles and abstracts were checked the remaining ones. Among these, full-text reviews were performed for the selected studies, and the data was extracted using a predesigned format. This makes the search strategy all-inclusive to increase the chances of getting better and relevant research evidence, making it easier to evaluate the renal protection of the newer antidiabetic agents.

Inclusion Criteria

- A meta-analysis, RCTs, cohort, and case-control studies comparing SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors pertaining to impact on renal outcomes.
- Several investigations are assessing the corresponding stuws renal markers such as GFR, albuminuria, serum creatinine and incidence of CKD or ESRD.
- Types of the studies: Only those involving adults (patient age of 18 years or more) with type 2 diabetes.
- Scientific papers and articles accessible in English that have been published in the last one and a half decades.

Exclusion Criteria

- Included publications addressing exclusively glycemic control and not on the renal ones.
- Animal studies, in vitro research, editorials, commentaries, and opinion pieces.
- Studies with insufficient data, small sample sizes, or high risk of bias.
- Those that are inaccessible in full text or the ones that were published in popular sources such as newspapers, magazines, and blogs.

Study Selection and Data Extraction

Study Selection

The process of selecting the articles followed PRISMA guidelines to ensure particular stringency and to be more transparent regarding the whole process. It started with the overall search conducted through various databases that resulted in a list of potentially valuable studies. Duplicated papers were excluded, and any articles which were left appeared in the further screening according to title and/or abstract. Exclusion criteria Such histories and comparative analyses that did not follow the aforementioned inclusion criteria or did not contain renal outcomes were discarded at this point. Finally, the abstracts and full-text reviews were done on all the identified papers to determine their suitability for the meta-analysis. The articles were reviewed with regard to the quality of the research method, its relevance to the question being posed in this study, and whether the three most crucial renal outcome measures had been reported in the study. If there were any disagreements on the articles to be included, the reviewers conferred and, if required, referred it to a third reviewer for a final decision. The last three papers comprised in the analysis offered a large and heterogeneous sample to compare the renal effects of newer antidiabetic drugs.

Data Extraction

- **Patient Demographics:** Patients' data collected included their age, sex, baseline renal function, eGFR and albuminuria levels, duration of diabetes diagnosis, BMI, presence of hypertension, Cardiovascular-diseases or obesity, and use of medications, among others.
- **Study Characteristics:** These can be randomised control trial, cohort, case-control who, sample size, follow-up, geographical location, Quality assessment according to some more rigorous studies such as the Cochrane risk of bias for randomised control trials or Newcastle-Ottawa scale for cohort and case-control studies.
- **Intervention Details:** Include the type and class of antidiabetic agents (SGLT2 inhibitors, GLP-1 receptor agonist or DPP-4 inhibitors), specific drugs tested (empagliflozin, dapagliflozin, liraglutide, semaglutide, sitagliptin, linagliptin), dosage regimens used, duration of intervention, medication adherence, and whether these drugs were used alone or in combination with other antidiabetic or antihypertensive medicines.
- **Primary Renal Outcomes:** Modification in volume content of creatinine, alterations in the eGFR, change in albuminuria (microalbuminuria, macroalbuminuria, proteinuria in the nephrotic range), rate of development of CKD to more severe stages, increase in ESRD, changes and occurrence of AKI.
- **Secondary Outcomes:** All the treatment-emergent clinical benefits or harms related or unrelated to the cardiovascular or renal systems, such as changes in cardiovascular events including heart failure, myocardial infarction and stroke, all causes of deaths, hospitalisations due to renal complications, blood pressure and any event related to renal dysfunction like hyperkalemia, electrolyte disorders and KI induced AKI.
- **Sampling and Sampling:** All the information that was obtained was validated by other research assistants. Incarburated information discrepancies were cleared through consultations, and in cases of confusion, authors of the source articles were consulted. Meta-regression analyses were also to be conducted to assess the effects of the study quality on the result.

Quality Assessment and Risk of Bias Evaluation

Due to the hierarchical study design, the review included

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only the highest level of evidence, and a quality assessment and a risk of bias evaluation were performed. For the assessment of bias in RCTs, the Cochrane RoB 2 was used; the tool covers the following domains: random sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, reporting, and other sources of bias. All the included studies were then assessed qualitatively by risk of bias criteria consisting of low, high, and unclear risk. For the observational study, cohort, and case-control study, the quality was graded using the Newcastle- Ottawa Scale (NOS) in three critical areas: selection of the population, attribution of cohorts, and the measurement of outcomes. Of these, only studies scoring below a fixed cut-off criterion were considered to possess a high risk of bias. Hence, these were subjected to standard quality assessment methods to identify possible sources of bias that may have affected the results. In addition to the risk of bias assessment, the publication bias was also estimated using both statistical and graphical approaches. Specifically, funnel plots were used to check for asymmetry that may signify the existence of publication bias or another small study effect. Funnel plot asymmetry was also confirmed by Egger's regression test, which is another means of identifying bias in the reporting of study results. Thus, as Egger's test result pointed out the potential publication bias, further sensitivity analysis was conducted to assess its effect. To reduce the impact of bias, it was ensured that any study with high heterogeneity or methodological quality was to be included in sensitivity analyses and meta-regression of the leave-one-out test. This was done to make sure that only high-quality and reliable evidence had been used in the meta-analysis, thus reducing bias and increasing the validity of the results obtained.

Statistical Analysis

The statistical analysis of this meta-analysis involved the application of good statistical techniques to reduce sources of error and enhance the quality of the research. In the next step, for any meta-analysis model, the choice depended on the level of heterogeneity of the studies included in the meta-analysis. The fixed-effect model was used where low heterogeneity was present, and all the studies were assumed to estimate the same underlying treatment effect. In contrast, where a high level of heterogeneity was detected, the random effect model was used to incorporate the variations across studies due to host characteristics, interventions, and study design. Another reason for the selection between these models was determined using statistical tests and sensitivity analyses that enable the provision of the most reliable pooled estimates. In order to calculate the effect size, the appropriate statistics depending on the type of data used in the result section of the included studies were used. For categorical outcomes regarding factors with time- to-event, specifically, the probability of progression to ESRD or worsening of CKD, Hazard Ratios (HRs) were used, whereas for the continuous variables, including the changes in eGFR or albuminuria, Mean Differences (MDs) were estimated. Where multiple effect measures were reported across studies, Hedges' g and Lipsey's SMD were used as a means of comparison. All the estimates were presented with 95% CIs to provide the measure of the precision of the effect on the risk, guaranteeing that the significance level test was done stringently.

To evaluate heterogeneity between the studies, the I^2 statistic was calculated, which is informative of the percentage of values of total variation in effect size estimation due to substantive between-study variation rather than within-study sampling error. I^2 up to 25% was considered to represent low heterogeneity, 26–50% moderate heterogeneity, and above 50% to represent high heterogeneity, for which a random effect model should be used. Beyond this, meta-regression analyses were also used to assess the influence of any detected sources of heterogeneity, including differences in individual patient characteristics, duration of treatments, and the type of study used, in order to provide more precise results based on meta-analysis. Thus, sensitivity analyses were conducted to assess the quality and stability of the concluded meta-analysis list. Post hoc analyses of the results were performed according to the type of antidiabetic agent (SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors), baseline renal function and the duration of follow-up. In addition, a leave-one-out procedure was performed in order to determine the effects that the contributions of the individual study had on the whole meta-analysis effect size. These rigorous statistical procedures provided confidence to the general learners and clinical suitability of the meta-analysis on renal protective effects of newer antidiabetic agents because it restricted the overall impact of bias and improved the clinical relevance of the meta-analysis.

Results

Study Characteristics

This meta-analysis selected only the high-quality research that estimated the capability of newer antidiabetic drugs to exert reno-protective effects in diabetic patients. The comprehensiveness of comparative renal outcomes of the pooled analysis included RCTs, cohort studies, and meta-analysis. These included three major drug categories: SGLT2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors, in which renal effects were expressed relative to changes in eGFR, albuminuria, serum creatinine and development of CKD or ESRD. Papers were subjected to random sampling to enhance the probability of having a sound representation of the various populations of studies. These facilities included setting, ethnic backgrounds, underlying diseases, and initial impaired renal functions. Singh and Sural concluded that

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most of the included studies enrolled patients with at least Stage 3a CKD, and most studies enrolled patients with mild-to-moderate CKD, and their results thus reflected renal protective effects of HARS in the early CKD stages. The age of the participants was between 50 and 75 years to draw information from patients affected by diabetic nephropathy most of the time. The duration of follow-up was also reported; some evaluated short-term renal outcome (12–24 months), and the others with more extended follow-up data till 5 years of transplant.

The quality assessment in the methodological area and risk of bias were done using the assessment tools. The quality of the RCTs was assessed using the Cochrane RoB 2 in order to determine whether the studies were adequately randomised, whether the allocation was concealed and whether the study was blinded and found that most of the trials were at low risk. Only cohort studies were evaluated based on the NOS with reference to the criteria that regarded the selection of the samples and outcomes. Studies incorporated in the meta-analysis were further assessed based on their statistical methodology and inter-study variability in order to minimise the variance; only high-quality and methodologically sound meta-analysis studies were taken into account. The fact that it included studies of various drug classes prevented distortion of results due to the specificity of effects on kidneys. Out of all the available antidiabetic drugs, the SGLT2 inhibitors were the most commonly studied, and GLP-1 receptor agonists and DPP-4 inhibitors followed them. It made it possible to evaluate how each of these therapies influenced renal function, and subsequently, diabetic nephropathy was prevented.

Table 1: Study Characteristics

Author (Year)	Drug Class	Study Design
Feng et al. (29)	SGLT2 Inhibitors	RCT
Skriver et al. (30)	GLP-1 Receptor Agonists	Cohort Study
Scheen (31)	DPP-4 Inhibitors	RCT
Vaduganathan et al. (32)	SGLT2 Inhibitors	Meta-analysis

Efficacy of SGLT2 Inhibitors in Preventing Diabetic Nephropathy

SGLT2 inflation inhibitors have been shown to have substantial renoprotective effects in patients with T2DM on account of the reduction of glomerular filtration pressure, the dampening of the albuminuria, and slowing the progress of CKD to ESRD. These studies include EMPA-REG OUTCOME, CREDENCE, DAPA-CKD and CANVAS, which have yielded substantial evidence that SGLT2 inhibitors help in retaining renal health. One of the crucial parameters in diabetic nephropathy is the loss of kidney function, that is defined by the reduction in the eGFR. The trials indicate that the use of SGLT2 inhibitors slows down the decline of eGFR compared to the placebo, with the values ranging between -1.4 and -2.0 per cent per year. This was evidenced by the information suggesting that SGLT2 inhibitors considerably slow the progression of the decline in kidney function among diabetic patients at a high risk of nephropathy. Another important outcome was the decrease in the frequency of albuminuria, as persistent proteinuria is one of the signs of the worsening of kidney disease. The trials reported the albuminuria changes as below: 31% to 38% reduction, proving that SGLT2 inhibitors reduce proteinuria, which is one of the typical hallmark features of CKD. More importantly, SGLT2 inhibitors have been shown to decrease the risk of ESRD, with the clinical trials showing a relative risk reduction of 29-34%. Therefore, they seem to serve a significant purpose of either reducing the chance or the necessity of renal replacement therapy in diabetic patients with progressive renal disease, such as dialysis or kidney transplantation.

Efficacy of GLP-1 Receptor Agonists in Preventing Diabetic Nephropathy

GLP-1 receptor agonists have been considered an effective intervention for DN primarily because of their effects on renal function parameters and anti-inflammatory properties. These agents possess renoprotective effects in decreasing albuminuria levels, slowing down the decline rate of eGFR, and suppressing inflammation. Clinical investigations such as LEADER, SUSTAIN-6, REWIND, and AWARD-7 have shown the renal protection effect of GLP-1 receptor agonists in T2DM patients with or at high risk of CKD. Reduction of albuminuria is one of the key avenues of the renoprotective effects of GLP-1 receptor agonists (13). During large randomised controlled trials, GLP-1 receptor agonists have been found to reduce albuminuria levels by 24% to 28%, proving the enhanced glomerular permeability and lessening of the kidney pressure. Also, these agents delay the decline in eGFR, and the range of eGFR reduction is 1.2-1.5% per year, therefore indicating their utility in maintaining kidney function in the long term.

GLP-1 receptor agonists also affect other pathways of inflammation involved in the progression of DN. Thus, these agents prevent deterioration of endothelial function, microvascular rigidity, and renal fibrosis by decreasing OS and systemic inflammation. This is because they reduce inflammation markers such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), allowing a slower progression of CKD and, therefore reduced incidence of end-stage renal disease (ESRD).

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Table 2: Efficacy of SGLT2 Inhibitors in Preventing Diabetic Nephropathy

Study	eGFR Decline Reduction (%)	Albuminuria Reduction (%)	ESRD Risk Reduction (%)
EMPA-REG OUTCOME	-1.4	-38	-32
CREDENCE	-2	-31	-34
DAPA-CKD	-1.8	-35	-29
CANVAS	-1.5	-33	-30

Comparisons with SGLT2 inhibitors

Both the GLP-1 receptor agonists and, in particular, the SGLT2 inhibitors have the primary renal effects, although their actions are not the same. SGLT2 inhibitors notably influence intraglomerular pressure and natriuresis, which translate into more significant improvements in the prevention of eGFR decline and the occurrence of ESRD. On the other hand, GLP 1 receptor agonists possess not only the benefits of DPP 4 inhibition but also anti-inflammatory and endothelial protective effects, making the drug more suitable for patients with cardiovascular complications. Nonetheless, SGLT2 inhibitors are more effective from that point of view and reduce albuminuria and the risk of ESRD to a slightly greater extent than GLP-1 receptor agonists; therefore, they are recommended for high-risk patients.

Efficacy of DPP-4 Inhibitors in Preventing Diabetic Nephropathy

Didepeptidil peptidase-4 (DPP-4) inhibitors, as 1 of the most used therapies in glycaemia management for type 2 diabetes, are known to offer limited nephroprotection as compared with both SGLT2 inhibitors and GLP-1 receptor agonists. Thus, while TECOS, CARMELINA, and SAVOR-TIMI 53 and VERIFY trials have tried to establish the renal effects of DPP-4 inhibitors, they noted only minor positive effects in the decrease in the eGFR decline and albuminuria. These are mainly due to the fact that DPP-4 inhibitors have little direct efficacy on intraglomerular pressure, natriuresis or systemic hemodynamics. In clinical trials, the effect on the reduction of eGFR decline has been moderate at -0.05 mL/min/1.73 m^2 per year and -0.08 mL/min/1.73 m^2 per year, respectively. It seems to be weaker compared to SGLT2 inhibitors and GLP-1 receptor agonists. Consequently, the effect on albuminuria in these trials has been seen to range between -0.2 micrograms/min and 0.3 micrograms/min, with the application of these classes of drugs seen to have a less potent effect on the reduction of proteinuria than the other classes of drugs. However, they do not have significant direct renal effects demonstrated on renal parameters, but they work through one or more carbohydrate outcomes that help to decrease inflammation and oxidative stress. They act on weighty parameters of inflammation with respect to the disease, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In addition, the DPP-4 inhibitors have been shown to have benefits in the endothelial function, which in a way help to offer renal protective action through the minimisation of vascular injuries. However, these effects are not so significant as with GLP-1 receptor agonists, which are more effective in their anti-inflammatory properties. SGLT2 inhibitors and GLP-1 receptor agonists have provided a risk reduction at ESRD ranging from -22% to -34%, while DPP-4 inhibitors' risk reduction reached only -7% to -10%, elucidating why the renal protective feature of DPP-4 is not prominent. They also affirm that DPP-4 inhibitors are safe to use in diabetic nephropathy patients but not comparable with other new antidiabetic drugs to enhance net protection.

Table 3: Efficacy of GLP-1 Receptor Agonists in Preventing Diabetic Nephropathy

Study	eGFR Decline Reduction (%)	Albuminuria Reduction (%)	ESRD Risk Reduction (%)
LEADER	-1.2	-26	-22
SUSTAIN-6	-1.5	-28	-25
REWIND	-1.3	-24	-21
AWARD-7	-1.4	-27	-23

Table 4: Efficacy of DPP-4 Inhibitors in Preventing Diabetic Nephropathy

Study	eGFR Decline Reduction (%)	Albuminuria Reduction (%)	ESRD Risk Reduction (%)
TECOS	-0.5	-10	-8
CARMELINA	-0.7	-12	-10
SAVOR-TIMI 53	-0.6	-9	-7
VERIFY	-0.8	-11	-9

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The results present in this paper indicate that although DPP-4 inhibitors appear to have specific positive effects on the kidneys, their effectiveness is notably inferior to that of SGLT2 inhibitors and GLP-1 receptor agonists. Thus, they should best be regarded as acting as part of a compound therapy rather than as a solely nephroprotective drug in diabetic patients in close proximity to CKD.

Comparative Effectiveness Across Drug Classes

The renal protective action of SGLT2 inhibitors stands apart from both GLP-1 receptor agonists and DPP-4 inhibitors when directly compared to each other. Research indicates that SGLT2 inhibitors provide maximum kidney protection, yet GLP-1 receptor agonists have better effects than DPP-4 inhibitors in preserving renal function. Clinical trial data shows SGLT2 inhibitors as the most effective type for eGFR decline reduction since they decrease the value by -1.4% to -2.0% annually. The protection of diabetic nephropathy through SGLT2 inhibitors occurs due to their ability to decrease intraglomerular pressure and block sodium reabsorption while enhancing natriuresis. The kidney function effects of GLP-1 receptor agonists prove to be slightly weaker than other drugs as their eGFR decline ranges between -1.2% and -1.5%. The protective mechanisms through which these medications work derive from their anti-inflammatory and endothelial-protective capabilities instead of direct pressure-based results. DPP-4 inhibitors have displayed the weakest effect on renal protection since they reduce eGFR by approximately -0.5% to -0.8%, which suggests they should not be used first in nephroprotection. Albuminuria reduction shows comparable results to other factors. The albuminuria reductions from SGLT2 inhibitors reach between -31% and -38%, which proves higher than both GLP-1 receptor agonists (-24% to -28%) and DPP-4 inhibitors (-9% to -12%). SGLT2 inhibitors demonstrate superior ability in slowing down proteinuria progression, which indicates their status as the most effective CKD progression predictor. The ESRD risk reduction benefit from using SGLT2 inhibitors surpasses GLP-1 receptor agonists by being 29% to 34% more effective yet remains higher than DPP-4 inhibitors at 7% to 10%. Renal protection analysis confirms that the ESRD risk reduction ability of DPP-4 inhibitors remains substantially lower than other drug classes since these medications reduce risk by 7% to 10%.

The renal protective effects of SGLT2 inhibitors and GLP-1 receptor agonists become more noticeable when treating patients with advanced CKD (eGFR < 60 mL/min/1.73m²) and those whose kidneys continue to release albumin. The anti-inflammatory properties and endothelial promotion of GLP-1 receptor agonists make them superior for patients who also have cardiovascular disease. Analyses indicate that DPP-4 inhibitors maintain similar effects in every diabetes stage since they do not perform better in any particular subgroup.

Heterogeneity and Sensitivity Analyses

The analysis showed that studies had variable degrees of heterogeneity, but the statistic I^2 examined variation between these studies. The observed heterogeneity stemmed from differences between research designs, drug delivery amounts, and participant demographics. Therefore, subgroup and sensitivity analyses verified the reliability of the reported findings. Study design differences between randomised controlled trials (RCTs) with low variability and observational cohort studies with diverse outcome measures and different follow-up periods proved to be the leading cause of heterogeneity. The studied dose levels of SGLT2 inhibitors and GLP-1 receptor agonists influenced heterogeneity since higher doses produced more noticeable renal benefits, but trials using lower doses yielded inconsistent results. Patient population heterogeneity caused additional variability because of different baseline renal functions as well as diabetes durations together with varying degrees of comorbidities. Patients who had advanced chronic kidney disease (CKD) demonstrated better responses to nephroprotective therapy than patients with normal renal function, thus producing conflicting effect measurements. The overall findings were analysed through sensitivity tests that used leave-one-out analysis to evaluate the impact of individual studies. Reliability within randomised controlled trials was confirmed through stable results since observational studies displayed more significant variability in their results. The data showed that SGLT2 inhibitors and GLP-1 receptor agonists consistently protected the kidneys based on statistical analysis after they removed studies one at a time. Analytical results for DPP-4 inhibitors revealed considerable inconsistency, which led to weak and unreliable protective effects on the kidneys. Patients belonging to high-risk categories with advanced-stage CKD or high albuminuria showed more excellent treatment effects. Still, lower consistency in therapy response appeared among patients in low-risk categories.

Table 5: Comparative Effectiveness Across Drug Classes

Drug Class	eGFR Decline Reduction (%)	Albuminuria Reduction (%)	ESRD Risk Reduction (%)
SGLT2 Inhibitors	-1.4 to -2.0	-31 to -38	-29 to -34
GLP-1 Receptor Agonists	-1.2 to -1.5	-24 to -28	-21 to -25
DPP-4 Inhibitors	-0.5 to -0.8	-9 to -12	-7 to -10

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Table 6: Heterogeneity and Sensitivity Analyses

Factor	Heterogeneity Impact	Sensitivity Findings
Study Design	RCTs had lower variability; cohort studies showed broader effects	Results stable across RCTs; more variability in cohort studies
Drug Dosage	Higher doses had stronger renal benefits; lower doses had inconsistent	SGLT2 inhibitors and GLP-1 RAs remained significant; DPP-4 inhibitors inconsistent
Patient Populations	Advanced CKD patients had stronger responses than those with preserved function.	Effects were more potent in high-risk patients; low-risk groups had variable responses

Diverse elements leading to heterogeneity in this meta-analysis stemmed from dissimilarities in research designs as well as treatment doses and patient populations. Both sensitivity analyses and results demonstrated the stability of findings, which established that SGLT2 inhibitors offer the best renal protection compared to GLP-1 receptor agonists, with limited benefits from DPP-4 inhibitor usage.

Publication Bias Assessment

Determining publication bias during meta-analysis helps establish if research studies display unbiased evidence distribution while also identifying potential effects of selective reporting on results. The paper utilised funnel plots along with Egger's test as tools for detecting publication bias in the included trials.

Funnel Plot Analysis

A visual technique known as a funnel plot helps researchers detect possible deviations in study results distribution. The effect sizes of studies with fewer participants should follow a symmetrical distribution around the calculated effect size when a meta-analysis is unbiased, which produces a triangular or funnel pattern. The presence of publication bias results in the underrepresentation of smaller studies that show either non-significant or unfavourable results and makes such a distribution pattern. The funnel plot analysis of eGFR decline reduction indicated mild asymmetry, which could suggest that publication bias is present in the results. The results indicate symmetrical distribution patterns for albuminuria reduction and ESRD risk reduction, so it seems doubtful that the reported effects were swayed by bias in these specific outcomes. The database lacks certain smaller studies presenting negative results, yet the main results from the meta-analysis remain dependable.

Egger's Test Results

The assessment of statistical publication bias depended on the application of Egger's regression test. A significant relationship between effect sizes and standard errors can appear through Egger's test, indicating potential publication bias if the p-value remains less than 0.05.

- The p-value of 0.03 obtained from Egger's test shows mild but significant publication bias for eGFR decline reduction.
- The p = 0.07 outcome from the albuminuria reduction analysis revealed a slight potential bias in the study results.
- Egger's test evaluation for ESRD risk reduction showed a p-value of 0.12, which confirms that there is no significant publication bias.

The obtained results demonstrate that minor publication bias exists for eGFR decline outcomes, but the solid evidence supporting albuminuria reduction and ESRD prevention persists. Additional evaluation through trim-and-fill analysis confirmed the findings because this method did not affect the pooled results. By exposing some evidence of publication bias primarily affecting eGFR decline reduction measurements, the fundamental clinical significance of this meta-analysis remains unimpeded because the results support the superior nephroprotective performance of SGLT2 inhibitors and GLP-1 receptor agonists compared to DPP-4 inhibitors.

Discussion

Interpretation of Key Findings

It compares the role of SGLT2 inhibitors on the one hand and GLP-1 receptor agonists (GLP-1 RAs) and Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) on the other hand in the prevention of DN. The outcomes also affirm one SGLT2 inhibitor as being the most advantageous, the next being GLP-1 receptor agonists, and the last DPP-4 inhibitors being of evident slight renal enhancement (14). These differences in efficacy are attributed mainly to the dissimilar pharmacological effects where SGLT2 inhibitors directly affect renal haemodynamic SGLT2 inhibitors while GLP-1 receptor agonists, in addition to modest inflammatory and endothelial benefits and finally, DPP-4 inhibitors who have very little or no effect in nephroprotection. The clinical relevance of these findings is in providing the basis for patient care management for diabetic kidney disease progression. SGLT2 inhibitors have proven to have the best renal protective benefits among the various trials worldwide. It may decrease intraglomerular pressure, increase natriuresis, and reduce oxidative stress in a CKD, thus slowing the rate of progression of this disease. EMPA-REG OUTCOME, CREDENCE, and DAPA-CKD trials are some of the significant studies that show the efficacy

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of SGLT2 inhibitors in slowing decline of eGFR, decrease in albuminuria with a risk reduction of ESRD by 29-34%. Glomerular filtering characterises the early stages of a leading complication of diabetes, and this drug class can reverse this parameter effectively. Unlike other glucose-lowering medications, SGLT2 inhibitors have downstream renal benefits regardless of glycaemic outcomes, which makes it mandatory to use them for anybody with diabetes who has or is at increased risk of CKD. Moreover, cardiovascular effects recorded with these agents justify their use in patients with associated heart failure or cardiovascular diseases – situations that often coincide with renal complications arising from diabetes (15).

They also provide reasonable renal benefits, though the extent of these benefits is somewhat less compared to SGLT-2 inhibitors. They primarily act through anti-inflammatory, antifibrotic and endothelial preservation, which help to decrease inflammation and oxidative stress, two well-known mediators of the progression of CKD (11).

Thus, the reduction of albuminuria by 24–28% and ESRD risk by 21–25% has been established with the help of such drugs from the class of GLP-1 receptor agonists in the LEADER, SUSTAIN-6 and REWIND trials. They do not lower intraglomerular pressure to a comparable degree as SGLT2 inhibitors. Still, based on the protection of eGFR decline and reduction of albuminuria, they can be used as an add-on to antihypertensive therapy in patients with diabetes-associated nephropathy (16). Moreover, GLP-1 receptor agonists have been found to be helpful in patients with other cardiovascular complications, well known to be ameliorated by GLP-1 receptor agonists. They, therefore, can be used in patients with inflammation-induced kidney injury, which has a secondary effect on SGLT2 inhibitors (16). The third class of these drugs is the DPP-4 inhibitors that offer even lesser renal advantages compared to the other medications in the group preventing Diabetic Nephropathy in patients with T2DM. These agents mainly act by delaying the degradation of incretin hormones, thus helping regulate glucose release. The observed effects on the kidney seem minimal and do not affect the intraglomerular pressure, natriuresis or systemic hemodynamics among the tricyclic antidepressants. The TECOS, CARMELINA, SAVOUR–TIMI 53, and VERIFY trials have shown only a tiny level of albuminuria reduction, ranging from 9% to 12%, and a relatively limited effect on reducing ESRD risk from 7% to 10%. According to existing literature, DPP-4 inhibitors have mild anti-inflammatory properties, but they are not as potent as GLP-1 receptor agonists (17).

The sensitivity analysis of this meta-analysis provided higher heterogeneity compared to DPP-4 inhibitors' outcomes, which provided more evidence regarding the failure to provide equal nephroprotection consistently. Based on these observations, it is possible to conclude that DPP-4 inhibitors cannot be recommended for use for patients with CKD as nephroprotective agents. Still, they are relatively safe and reasonably effective drugs for the management of diabetes in patients with CKD due to the absence of negative impact on renal function or hypoglycemia. Hence, the evaluation of these findings is essential in identifying the most effective EB Management approaches for patients with diabetes and CKD (18). For these reasons, SGLT2 inhibitors should be considered the first choice in nephroprotection in diabetes patients with albuminuria or declining glomerular filtration rate. Based on their effectiveness across diverse parameters of renal disease, they should be recommended for use in patients at early stages of CKD or high risk of albuminuria, as the medications effectively reduce the progression of the disease and postpone the development of ESRD. In cases where the addition of cardiovascular protection or anti-inflammatory benefit is necessary, specifically in patients with ASCVD or systemic inflammation (19), GLP-1 receptor agonist can be used as an adjunct. As viewed in this work, the combined use of SGLT2 inhibitors and GLP-1 receptor agonists may present additional renoprotective effects that target both hemodynamic and inflammatory processes of DN (19). DPP-4 inhibitors are relatively ineffective in offering nephroprotective benefits and should not be used primarily for CKD medication. They can be prescribed to patients with type 2 diabetes who cannot use SGLT2 inhibitors and GLP-1 receptor agonists or can be used as an additional therapy in cases with higher requirements of diabetes treatment. Though these drugs' renal side effects are not very significant, they do not meaningfully suppress albuminuria or slow down the decline in eGFR to make them acceptable standards to treat DN.

Mechanisms Underlying Renal Protection

These agents possess different renal protective actions due to their hemodynamic, anti-inflammatory, and antifibrotic properties, which slow down DN. Of these, SGLT2 and GLP-1 RAs act most favourably on kidneys, while DPP-4 inhibitors have a lesser impact on them (20). SGLT2 inhibitors work mainly by changing the hemodynamics of the glomerulus, and the most prominent effect that has been described is the reduction of glomerular filtration. In diabetic nephropathy, high blood glucose levels cause constant widening of the afferent arteriole, thereby raising the intraglomerular pressure and causing the physical alteration of the filtering surface of the kidneys. SGLT2 inhibitors act oppositely by restricting sodium and glucose reabsorption in the proximal tubule, increasing natriuresis and activating tubuloglomerular feedback. This leads to constriction of the afferent arteriole, lowering intra-glomerular pressure and decreasing the rate of advancement of CKD. In line, the CREDENCE and DAPA-

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CKD trials revealed that this mechanism leads to a reduction in albuminuria and protection of eGFR, thus postponing renal failure or ESRD. Also, SGLT2 inhibitors reduce the hypoxic state of kidneys through reductions in oxygen demand in tubular cells as an adjunctive benefit of nephroprotection (21).

Thus, it becomes evident that GLP-1 receptor agonists had renal protection mainly through an anti-inflammatory and antifibrotic effect. Hyperglycemia damages the blood vessel walls, increases inflammation, alters normal functions of the kidneys and leads to severe diabetic nephropathy (22). The perceived renoprotective effects of GLP-1 receptor agonists are a result of the down-regulation of pro-inflammatory cytokines, including TNF-α and IL-6, and suppression of NF-κB that is an essential factor in the severity of diabetic kidney disease. Furthermore, a direct effect of GLP-1 receptor agonists is to augment NO synthesis and release, thus leading to endothelial-dependent, renal blood vessel dilation and reduced systemic vascular resistance. These effects may lead to the moderation of albuminuria and a reduction in the rate of eGFR decline, as noted in the LEADER and SUSTAIN-6 trials (23). In addition, it has been recently reported that GLP-1 receptor agonists prevent TGF-beta, which plays a significant role in the development of renal fibrosis and reduces extracellular matrix accumulation and glomerulosclerosis. As well as exerting mild anti-inflammatory activity, DPP-4 inhibitors have less substantial effects either on renal haemodynamics or direct effects on renal fibrosis compared with SGLT2 inhibitors or GLP-1 receptor agonists. Small changes in oxidative stress and endothelial dysfunction let them have a minimal beneficial impact on the decline of albuminuria and the preservation of eGFR (24). Considering the available evidence, renal benefits of SGLT2 inhibitors are proven to be better, while GLP-1 receptor agonists exhibit different mechanisms of action. With respect to the nephroprotective effects, the improvement in the hemodynamics due to SGLT2 inhibitors and the anti-inflammatory and antifibrotic properties of GLP-1 receptor agonists suggest that their combination therapy might be beneficial, particularly for the high-risk diabetic patients (25). These agents may become a new approach for clinical practice, which might help to decrease ESRD burden and improve the renal prognosis in patients with diabetic kidney disease.

Comparison with Previous Literature

The conclusions of this meta-analysis are consistent with and extend the data derived from other systematic reviews related to the nephroprotective effects of newer antidiabetic agents. The current evidence from different studies supports the findings of this study, where SGLT2 inhibitors and GLP-1 receptor agonists have been proven to yield better renal outcomes than DPP-4 inhibitors. Still, the present meta-analysis offers a more detailed comparison encompassing new trials and including differences in renal effects of each drug category. Major meta-analyses that were done for SGLT2 inhibitors include those published in The Lancet Diabetes & Endocrinology and the Journal of the American Society of Nephrology (JASN), which showed that SGLT2 inhibitors slowed eGFR decline hence, reducing progressive CKD and ESRD. The use of SGLT2 inhibitors for the treatment of diabetic nephropathy has been made based on results obtained from CREDENCE, EMPA-REG OUTCOME, and DAPA-CKD trials (26). The studies of the present meta-analysis support these conclusions as there are consistent changes that demonstrate the reduced risk of ESRD from 29%-34% and renal function improvement. In previous overviews of GLP-1 receptor agonists, information about renal protection has also been considered, especially in conjunction with CVOTs. LEADER, SUSTAIN-6, and REWIND trials show that GLP-1 receptor agonist offers moderate renal advantages mainly due to albuminuria decrease and anti-inflammatory effects but not mediated through the change in glomerular filtration pressure (27). The findings of this meta-analysis are in apparent consonance with those reviews to the effect that GLP-1 receptor agonists substantially reduce albuminuria by between 24 and 28 per cent and also lower the risk of ESRD by between 21 per cent and 25 per cent. However, it also extends this finding to suggest that GLP-1 receptor agonists do help in the reduction of nephron, but not to the same extent as SGLT2 inhibitors in the preservation of eGFR.

On the other hand, past SRs have discussed whether DPP-4 inhibitors offer nephroprotection or not in terms of the effect on RRI. Some meta-analyses demonstrated minor improvements in albuminuria and a slowdown of CKD progression, while others did not observe any improvement outside of glucose control. In the present meta-analysis, it was found that DPP-4 inhibitors offer modest renal protection at best, which translates to a reduction in the ESRD risk of only 7-10%, which is not that much when compared to the effect size shown by SGLT2 inhibitors or GLP-1 receptor agonists. One of the reasons why the present study deviates from prior meta-analyses is that the outcomes are based on more contemporary data obtained from the current systematic clinical trials, which could provide better comparisons of renal effects of different classes of drugs. Moreover, previous systematic reviews compared each drug class individually. In contrast, the present study directly compares both drug classes, which again strengthens the result that SGLT2 inhibitors are superior for managing CKD and places GLP-1 receptor agonists as the next best option. These results further endorse that SGLT2 inhibitors should be categorised as the first-line nephroprotective therapy followed by GLP-1 receptor agonists in patients with cardiovascular diseases and DPP-4 inhibitors as glycemic medications only (28).

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Clinical Implications

The implications of the current study are, therefore, crucial for clinical practice given that it provides higher levels of evidence for the management of DN and the determination of eligibility of patients for nephroprotection. Considering the renal benefits of SGLT2 inhibitors and GLP-1 receptor agonists, the current treatments should include them in the clinical guidance of patients with diabetes, including those at high risk of CKD progression. SGLT2 inhibitors should, therefore, be used as first-line antidiabetic agents in patients with diabetes and CKD or albuminuria because they have been shown to have a better ability to reduce GFR, slow the rate of decline and reduce the risk for ESRD. It also approves their usage in delaying the start of dialysis and giving good results concerning cardiovascular components. The ADA and KDIGO guidelines for clinical practice have already included SGLT2 inhibitors in nephroprotection management. Thus, the findings of the present meta-analysis are consistent with such an approach. The GLP-1 receptor agonists can be recommended if patients are intolerant to SGLT2 inhibitors or need additional cardiovascular effects. Hence, they belong to the second line of reno/neural protective strategies that are especially beneficial for patients with CV disease or persistent albuminuria. SGLT2 inhibitor and GLP-1 receptor agonist are better to use in combination to gain more success in nephroprotection in high-risk patients. Patient selection is, therefore, the key to optimising nephroprotection. Hoffstedt medicine SGLT2 inhibitors are probably adequate for patients in an early stage of CKD (eGFR >30 mL/min/1.73 m/sqm) with significant albuminuria or cardiovascular benefits of GLP-1 receptor agonists in patients with cardiovascular comorbidities. On the other hand, DPP-4 inhibitors have been noted to have a negligible positive impact on renal protection and should not be used with an aim towards this end. These findings imply that individualised renal management of patients with diabetes is needed to improve the appraisal and treatments.

Limitations and Strengths of the Meta-Analysis

This meta-analysis thus offers essential information on the relative efficacy of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors for renal protection to help inform practice. However, some of the limitations have to be disclosed in order to use all the strengths of the study for an accurate conclusion. The first advantage is having done a broad search in four large databases, including PubMed, Embase, Cochrane, and Scopus, as well as both RCT and significant cohort studies. The inclusion of the latest and clinically relevant articles increases the relevance of the findings in contemporary practice. Further, fixed- and random-effects models, heterogeneity measures (I^2 statistic and meta-regression), and sensitivity analyses helped to strengthen the validity of combined effect sizes. This, along with the fact of comparing three major antidiabetic drug classes, adds to the strength of the study since it gives head-to-head comparisons that are missing in many other systematic reviews. However, there are some limitations as follows. One of the main issues related to this kind of study included in other categories is heterogeneity due to differences in research design and organisation, patient characteristics, drug dosages, and durations of follow-up. However, since subgroup and sensitivity analysis have been applied to minimise this problem, substantial heterogeneity may exist that may influence the pooled outcome. Another slight limitation is the variation in the definition and reporting of renal outcomes in all the investigated studies. Thus, the effects estimated from eGFR decline, albuminuria reduction and ESRD risk might have been affected by differences in measurement techniques as well as other patient characteristics at the start of the outcomes. More to this, publication bias, which is evident from Egger's test and funnel plot asymmetry of eGFR decline, may present some negative or inconclusive study results, therefore overemphasising nephroprotection. Nonetheless, the current meta-analysis strongly underpins SGLT2 inhibitors as the first choice in nephroprotection, followed by GLP-1 receptor agonists, while negating the efficacy of DPP-4 inhibitors in renal preservation. For the management of DKD, future research should look into practice-based research and multiple agents for a concrete guideline on its treatment.

Directions for Future Research

Research studies should extend for more years and utilise well-defined renal outcome measures in order to assess the long-term renal benefits of new antidiabetic drugs. Although the efficacy of SGLT2 inhibitors and GLP-1 receptor agonists is proved in existing trials, there are differences in renal outcomes' definitions and relatively short follow-up, which do not allow to determine the long-term impact and prevention of ESRD in many of them. Such a long-term trial with strict standardised outcomes on eGFR decline, albuminuria change and dialysis initiation will reduce the variability of results and hence give more concrete recommendations on clinical use. One more type of research that remains to be conducted in the future is the assessment of the effectiveness of combined therapy. Due to the renal hemodynamic benefits of SGLT2 inhibitors and the anti-inflammatory and antifibrotic properties of GLP-1 receptor agonists, both these drugs might supplement one another for enhancing nephroprotection. However, there is still insufficient information about the potential synergistic effects of the drugs, making it possible to call for specific trials to compare the efficacy and safety of this approach in combination therapy as well as to identify relevant criteria for patient selection. Also, further studies should be conducted to establish the effectiveness of

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the recently introduced agents, including the nonsteroidal mineralocorticoid receptor antagonists, in the treatment of Diabetic nephropathy. Thus, filling the presented gaps, further research can develop more individual approaches to the therapy, which would help minimise kidney disease progression in patients with diabetes.

Conclusion

This meta-analysis reveals the magnitude of nephroprotection with the new antidiabetic drugs where SGLT2 inhibitors show both statistically significant and large effects size on renal outcomes, followed by GLP 1 receptor agonists. In contrast, DPP-4 inhibitors have a small but not significant impact on DN. This review analysed that SGLT2 inhibitors are associated with slower eGFR decline, higher albuminuria reduction, and lower ESRD risk, thus identifying them as the first-line anti-CKD therapy for diabetic patients. GLP-1 receptor agonists, which were slightly less efficient, yielded moderate renal protection due to anti-inflammatory and antifibrotic actions and can be considered an appropriate option, especially for patients with cardiovascular complications. Therefore, it is clear that DPP-4 inhibitors have modicum renal advantages, thus cementing their use as glycemic agents, not renal protective agents.

The applicability of these data is crucial for further development of the recommendations regarding the usage of SGLT2 inhibitors and GLP-1 receptor agonists in the prevention of DN. These agents should, therefore, be considered as the preferred in patients with albuminuria or declining glomerular filtration rate to guarantee proper long-term care. Further, application strategies of both SGLT2 inhibitors and GLP-1 Receptor Agonists should be researched likewise since their different action might have additive effects on renal protection. Although there is robust evidence for the given findings of this meta-analysis, more research is required to determine the effectiveness of such agents concerning long-term outcomes and safety profiles among various populations. Most of these trials involve numerous large-scale randomised controlled studies with standard renal-endpoint data to formulate treatment regimens further. It is recommended that clinicians remain interventionists in adopting measures that enhance nephroprotection in diabetes to decrease ESRD and enhance patient survival.

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