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RENAL PROTECTIVE COMPARISON BETWEEN SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS VERSUS GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS: A SYSTEMATIC REVIEW

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Abstract

In the realm of diabetes, the therapeutic panorama has changed for chronic kidney disease with the emergence of SGLT2 inhibitors and GLP-1.

This research aims to conduct a comprehensive comparative analysis of the renoprotective effects of SGLT2 inhibitors and GLP-1 RAs in individuals with T2DM and renal complications and to provide comprehensive awareness of the mechanisms, efficacy comparison, and practical advice on visionary care for the management of CKD with T2DM.

2093 records from 2013 to 2023 were identified electronically using Google Scholar, MEDLINE, PubMed, and ScienceDirect databases. Grey material was also searched. RCTs and meta-analyses reporting renal composite outcomes, such as changes in eGFR, urinary albumin progression, and ERSD results after GLP-1 RAs and SGLT-2 inhibitors therapy in T2DM with CKD patients were included. HRs, RR, and 95% CI were calculated. Quality assessment was done using the AMSTAR-2 checklist.

The prevalence of renal composite outcomes and albuminuria was (33% to 36%) and (38% to 42%) in SGLT2i-treated patients respectively, compared to GLP-1RAs-treated patients (14% to 24%) and (10% to 20%) proportionately. The annual decline in eGFR (34% versus 15%) and UACR changes (38% versus 20%) was noted between the two groups. Progression to ESRD and serum creatinine also differed significantly in SGLT2i-treated patients than in GLP-1RA-treated patients.

The Preliminary findings from the data analysis indicate that both drug classes exhibit positive effects on renal function improvement, but SGLT2 inhibitors exhibit superiority over GLP-1 receptor agonists regarding renal outcome in T2DM patients with CKD. Further research is required to validate both drugs' efficacy in this population.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from insulin resistance and inadequate insulin secretion or both. Long-standing diabetes can lead to many complications, one of the most common is kidney disease. In the last two decades, approaches to treat diabetic kidney disease have evolved and new medications have been adopted in treatment algorithms especially SGLT2 inhibitors and GLP-1 receptor agonists. This thesis considers the need to compare and highlight the disparities between these two medicines in the context of diabetic kidney disease. Previously, insufficient research data was available to find a comparison between these medications concerning assessing kidney outcomes.

The commonness of T2DM globally has become a plague, imperiling approximately 537 million adults in 2021, and is anticipated to burgeon to 780 million by 2045. According to the international diabetic association, globally, one in every 10 adults is suffering from diabetes (IDA, 2023). According to (CDC, 2023) one in every 3 people with CKD has diabetes. DKD is a major public health burden with serious implications for healthcare costs and outcomes. (Jager *et al*., 2019)

The continuing and intensifying nature of T2DM leads to micro- and macro-vascular complications, including renal and cardiovascular disease. These complications, either individually or in combination, significantly contribute to premature morbidity and mortality among diabetic patients including life-threatening heart problems, total kidney failure necessitating dialysis, and premature death (Lui *et al*., 2022).

Despite advancements in diabetic treatments, the prevention and reversal of these diabetic complications remain inadequate, imposing an immense strain on the healthcare system. Consequently, there is an urgent need to develop more effective treatments.

Before two decades, the treatment options for managing renal complications in T2DM primarily focus on glycemic control, blood pressure management, and renin-angiotensin-aldosterone system (RAAS) blockade (Shami *et al*., 2023). Although these approaches offer some advantages in CKD patients, their effectiveness is limited, and necessitate different treatment methods required to decrease the adverse effects on kidney function.

As of late, two medicines have emerged as potential remedies to kidney issues in type 2 diabetes: SGLT2 inhibitors and GLP-1 agonists. Given the potential benefits of SGLT2 inhibitors and GLP-1 RA on renal function, it is crucial to inclusionary evaluate and compare their renoprotective effects.

In recent years, the emergence of SGLT2 inhibitors and GLP-1 RA as promising therapeutic options for individuals with T2DM and renal complications has raised questions regarding their comparative effectiveness in terms of renoprotection (Ghosal and Sinha, 2023).

While studies have demonstrated the renoprotective effects of both drug classes individually, there remains a significant research gap in understanding the relative efficacy, safety, and tolerability of SGLT2 inhibitors and GLP-1 RA in renal complications in T2DM. Addressing this research gap is paramount for clinical decision-making and improving patient outcomes.

This research addresses this void by performing an exhaustive assessment and juxtaposing the kidney-protecting impacts of SGLT2 inhibitors and GLP-1 RA in T2DM.

Ultimately, by bettering the handling of kidney problems in T2DM, our project can expand patient outcomes, cut healthcare charges, and relieve the load on healthcare systems.

This research project aims to systematically review and summarize the available evidence, organized as randomized controlled trials and meta-analyses conducted by researchers, on the renoprotective effects of SGLT2 inhibitors and GLP-1 RA in patients with type 2 diabetes mellitus (T2DM). By analyzing the ongoing work, the study aims to compare the renal efficacy of these drugs.

Through methodical appraisal and contrast, this exploration provides insights into their comparative efficacy in ameliorating renal function in patients with T2DM.

- The objectives of this review were
- To evaluate the impact of SGLT2 inhibitors and GLP-1 RA on renal function improvement.
- To assess the changes in eGFR associated with SGLT2 inhibitors and GLP-1 RA.

- To examine the reduction in albuminuria or adverse renal events with SGLT2 inhibitors and GLP-1 RA.
- To explore potential differences in safety and tolerability profiles between SGLT2 inhibitors and GLP-1 RA.

Literature Review

With the ascending dominance of type 2 diabetes mellitus established universally, there dwells a considerable correlation between type 2 diabetes mellitus and chronic kidney disease, expediting an augmented vulnerability to renal detriments and fatality (IDF, 2019). This literature review provides an exhaustive overview of the existing evidence regarding the benefits and limitations of SGLT2 inhibitors and GLP-1 receptor agonists in protecting kidney function in T2DM patients. The objective of the review is to summarize the information and provide a holistic understanding of the topic.

Definition and Classification of Diabetic Kidney Disease:

Diabetic kidney disease is commonly exhibited as worsening kidney function, the presence of albumin in the urine, and particular pathological structural changes determined by kidney biopsy (Khoury, 2020).

The extent to which diabetic nephropathy progresses relies upon estimations of the glomeruli's capacity to filter (eGFR) and the quantities of albumin (Albuminuria) present in one's urine. The classification of CKD is also based on these two elements.

Categorically, the eGFR is divided into 5 stages, and albumin in the urine is classified as normal, microalbuminuria and macroalbuminuria.

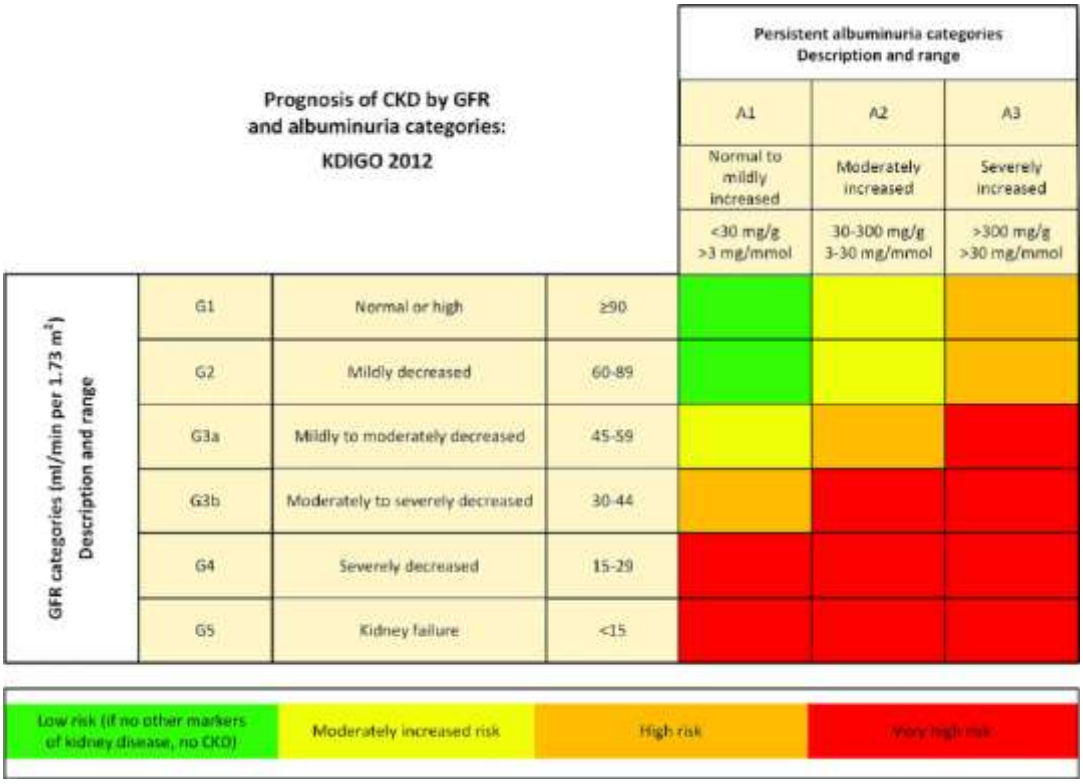

Figure 1: CKD categories by eGFR and Albuminuria

Pathophysiology of Diabetic Kidney Disease:

Persistent hyperglycemia is the crux of diabetic kidney disease, inducing multifactorial and complex mechanisms resulting in renal complications in T2DM. Constant high sugar leads to the activation of various biochemical routes, including renal hemodynamic changes, activation of the polyol pathway, the accumulation of last-stage glycation products, protein kinase C activation, increased oxidative

damage, and overacting RAAS. These procedures eventually lead to glomerular hypertension and sclerosis, thickening of the glomerular basement film, mesangial spread, and podocyte impairment (Brenner, 2001). Oxidative stress, derived from reactive oxygen products (Charlton, 2020) and the aggregation of advanced glycation end products (AGEs) leads to oxidative and inflammatory damage. (Zeng, 2019).

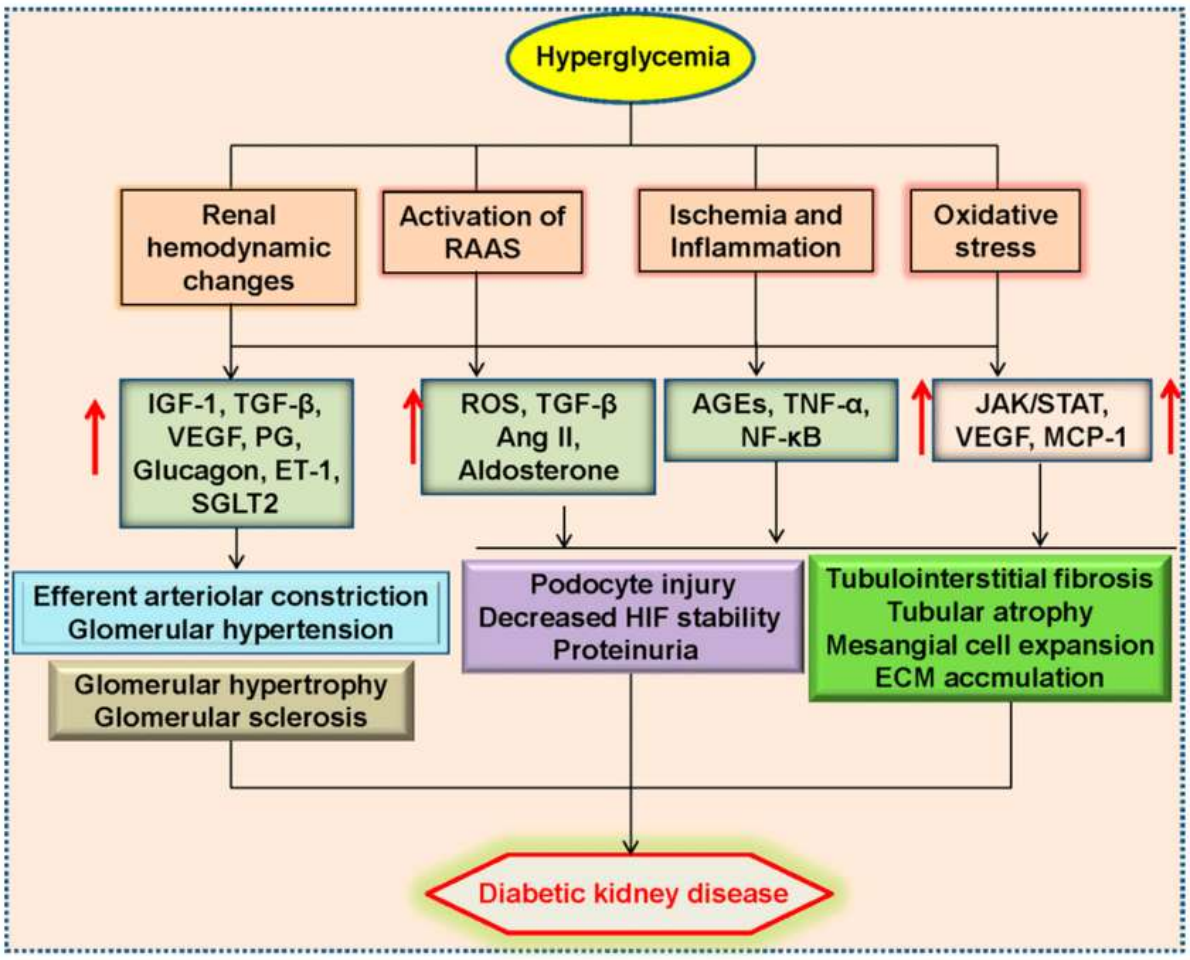

Figure 2: Pathophysiology of DKD

Remedial Significance of SGLT2 Inhibitors and GLP-1 RAs

Conventionally, previous guidelines of diabetes management concentrate on medication safety, effectiveness, cost, and drug intensification (Nathan et al., 2009). However, recent guidelines emphasize on early initiation of blood glucose control in newly diagnosed T2DM patients in reducing microvascular as well as macrovascular complications in T2DM patients. (Holman *et al*., 2014).

Since 2005, after FDA approved first GLP-1 RA, different cardiovascular outcomes trials (CVOTs) had been conducted for the evaluation of SGLT2 inhibitors and GLP-1 receptor agonists. (Goldfine, 2008). Moreover, the (FDA, 2020) acknowledges the beneficial effect of SGLT2 inhibitors and GLP-1 receptor agonists on cardiovascular and kidney disease.

The increasing prevalence of T2DM and its associated renal complications strains healthcare resources, productivity losses, and impact on quality of life necessitates exploring effective treatment options, to prevent disease progression, and to reduce the burden on healthcare systems (Berndt *et al*., 2021).

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2 inhibitors)

Generally, SGLT2 inhibitors works by targeting the renal glucose reabsorption pathway, chiefly in the proximal kidney tubules. Via blocking SGLT2 transporters, these drugs decrease the reclamation of filtered sugar, culminating in amplified sugar discharge in urine.

However, multiple pathways were identified to explain the renal protection effect of SGLT2 inhibitors. For example, by improving renal oxygenation, and decreasing inflammation in the kidney, increased natriuresis and tubule-glomerular feedback, SGLT2 inhibitors slow down kidney deterioration, irrespective of glucose control. (Neal *et al*., 2017).

The reduction in plasma glucose lead to improvements in insulin sensitivity and β-cell function. (Thomas, 2018**).** The increased glucose excretion also leads to a reduction in weight and adiposity. Furthermore, SGLT2 inhibitors are associated with increased sodium excretion (natriuresis), which restore solute delivery to the macula densa and reactivation of tubule-glomerular feedback leading to a reduction in glomerular hyperfiltration. In addition, because of their glucose-dependent mechanism of action, SGLT2 inhibitors have a low risk of hypoglycaemia. (Alicic *et al*., 2018).

SGLT2 inhibitors are associated with a rapid decline in urinary albumin regardless of glycemic control. This effect is attributed to the intra-glomerulus hydrostatic pressure changes, responsible for the rapid reduction in eGFR decline. (Cherney *et al*., 2017). Moreover, a sustained decline in eGFR and reduction in progressive albuminuria is noted after long-term use of SGLT2 inhibitors (Heerspink *et al*., 2017), also not related to blood glucose, weight or kidney status.

SGLT2 inhibitors are also responsible for blood pressure reduction (because of diuresis), weight loss, decrease in uric acid, and increasing red blood cell mass in the body. A decrease in blood flow to the kidney produces a state of low oxygenation within the kidney resulting in increased erythropoietin production and an increase in total RBCs in the blood.

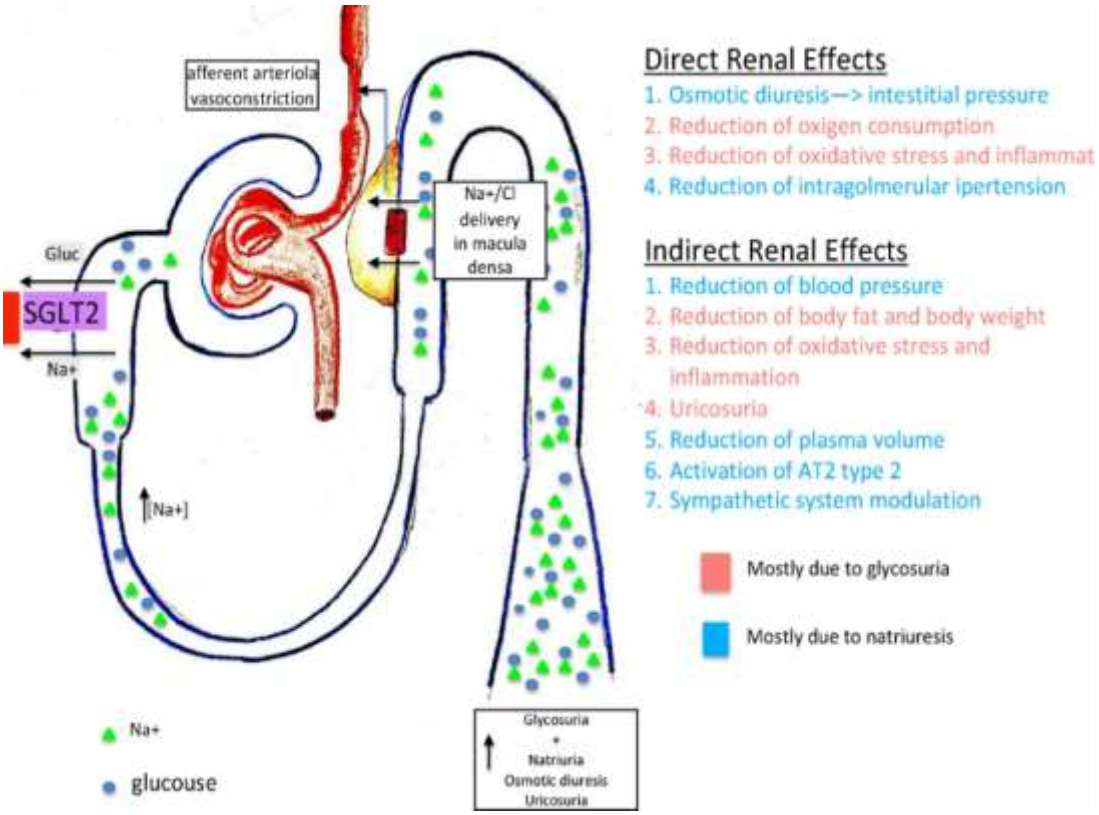

Figure 3: Mechanism of Action of SGLT2i

The pharmacokinetics of SGLT2 inhibitors vary slightly among different medications within the class. After oral administration, SGLT2 inhibitors are rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations achieved within 1-2 hours for most agents.

The decomposition of SGLT2 inhibitors occurs chiefly in the liver, through cytochrome P450 (CYP) pathway (Mima, 2022). The metabolites moulded are typically inert. Elimination of SGLT2 inhibitors occurs predominantly through renal excretion. The original substances and byproducts are primarily removed in the urine, with half of the drug amount to disappear ranging from 6 to 17 hours, depending on which particular drug (Berndt *et al*., 2021). As drug is removed by the kidneys, drug modifications are frequently needed for people with kidney disease.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

GLP-1 RA mimics the effects of glucagon-like peptide-1 (GLP-1), an incretin hormone secreted by the intestines in response to food intake. GLP-1 stimulates insulin secretion from pancreatic beta cells in a glucose-dependent manner, only when blood sugar levels are raised (Lui *et al*., 2022). GLP-1 receptor agonists stimulate GLP-1 receptors in many tissues of the body, including the pancreas, liver, gastrointestinal tract, and brain. This drug class promotes insulin secretion and suppresses glucagon release by the pancreas, resulting in glucose-dependent reductions in plasma glucose as well as reductions in postprandial glucose levels through inhibition of hepatic glucose production and delayed gastric emptying. (Van Baar et al., 2018)

In addition to delaying gastric emptying, GLP-1 receptor agonists act in regions of the brain associated with appetite and reward to induce satiety, which reduces food intake and promotes weight loss (DeFronzo, 2017).

Experimental evidence demonstrated that GLP-1RA exerts direct beneficial effects on kidney cells mainly by activating the cAMP/PKA signalling pathway in proximal tubular epithelial cells, which is involved in the pathogenesis of increased albuminuria, regulation of proximal tubule sodium reabsorption through NHE3, and reducing oxidative stress through NADPH (↓expression of inflammatory cytokines). GLP-1 RA mitigating the renin-angiotensin-aldosterone system through tubule-glomerular feedback leading to decrease in kidney disease progression (Nauck *et al*., 2017).

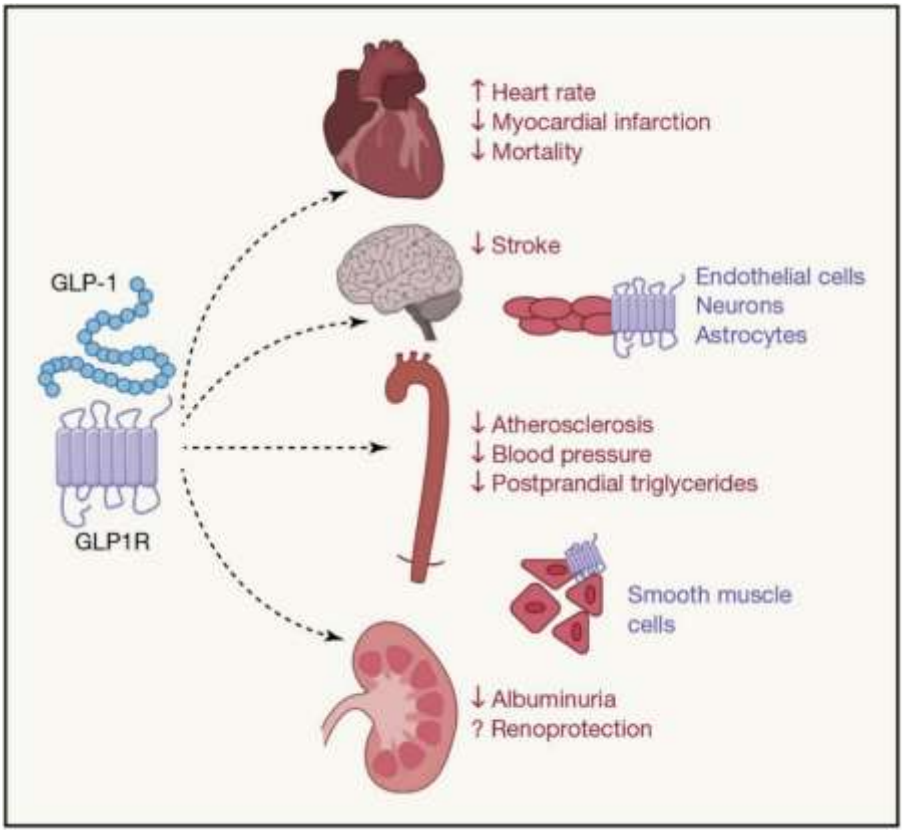

Figure 4: Mechanism of GLP-1Ras

GLP-1 RA is typically administered via subcutaneous injection. The assimilation percentage and physical availability of GLP-1 RA varies according to the different preparations. After absorption, these agents reach destinations like the pancreas and brain. Though ordinarily dismantled by the enzyme dipeptidyl peptidase-4 or DPP-4, the structures of GLP-1 RA shield them from such breakdowns, enabling their long-lasting impacts.
The removal of GLP-1 RA transpires through numerous pathways, including kidney clearance and liver breakdown. The precise method of removal and duration varies with each GLP-1 RA medication (Nagahisa and Saisho, 2019)**.**

Comparison of SGLT2 inhibitors and GLP-1 RAs
SGLT2i inhibits glucose and sodium transport via SGLT2 and GLUT 2 transporters which are responsible for 90% of glucose reabsorption thus inducing glucosuria, diuresis, natriuresis, and uric acid excretion. While GLP 1RA promotes diuresis and natriuresis via NHE3 receptors. Both, GLP 1RA and SGLT2i induce suppression of inflammatory markers such as TGFβ, IL6, TNFα, decreasing glomerulosclerosis, and tubulointerstitial lesions and causing afferent vasoconstriction. Both drugs' favourable effect is mediated exclusively through tubule-glomerular feedback. (Ninčević,2019)
GLP 1RA therapy leads to a decrease in RAAS activity causing efferent vasodilatation, Contrary to the effect of SGLT2 inhibitors, which increases RAAS activity due to natriuresis and volume depletion.
Notably, in the absence of any direct scrutinizes or oblique comparisons that have investigated the disparities betwixt these two medicament classes on renal consequences, it is difficult to deduce definitive inferences about their comparative effectiveness in safeguarding the kidneys.

Despite, the strong recommendations (ADA, 2021) that both drugs may shield the kidneys in people with T2DM. Still, some important differences were observed between these two drug classes.
In particular, the kidney effect of GLP-1 RA is constant among all the drugs in the same class, not like SGLT2 inhibitors, which showed diversity in results among the same drug class. Secondly, unlike SGLT2 inhibitors, GLP-1 RA can be safely used in CKD patients with moderate to severe CKD or even ESRD T2DM patients.

Nevertheless, SGLT-2i should be preferred in patients with heart failure or chronic kidney disease and albuminuria, while GLP-1 RA is a better choice in patients with low eGFR and with high-risk CVD or established ASCVD. However, due to differences in the mechanism of action, and side effects, both medications can be initiated in patients with CKD with diabetes.

A lack of understanding exists about directly analysing how SGLT2 blockers and GLP-1 receptor agonists shield the kidneys. Despite proof from separate experiments, determining how well they work compared to each other, how safe they are, and how well patients endure them is crucial.

METHODOLOGY

Search Strategy:

The literature search was conducted using multiple databases, including Google Scholar, PubMed, Medline, and Science Direct, to search relevant articles systematically from articles published during the last 10 years (from 2013-2023). The standard guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were followed. The MeSH words (Medical Subject Headings) were included in the search such as "Type 2 Diabetes" OR "Type 2 Diabetes Mellitus" AND "Sodium-glucose co-transporter 2 inhibitors" AND "Glucagon-like Peptide-1" AND "Chronic Kidney Failure" OR "ESRD" OR "Renal Failure, Chronic" AND "urine albumin"; "albuminuria" or "urine albumin or urine protein" or "proteinuria". In addition, drug names like "empagliflozin" AND "dapagliflozin" AND "canagliflozin" AND "ertugliflozin" AND "exenatide" AND "liraglutide" AND "lixisenatide" AND "semaglutide" AND "dulaglutide" AND "albiglutide"

AND "Efpeglenatide were also searched. The search was limited to randomized controlled trials (RCTs), and comparative meta-analysis studies.

Inclusion and Exclusion Criteria:
Those studies satisfying all of the following criteria were included in the present study:
I) Population: Studies including diabetic patients aged more than 18 years of age.
2) Intervention/Exposure: Studies that explored, demonstrated, or compared the effects of SGLT2 inhibitors and/or GLP-1 receptor agonists.
3) Comparison /Control: Studies that compared between SGLT2 inhibitors and/or GLP-1 agonists versus Placebo.
4) Outcome: Studies that reported the renal composite outcomes
Moreover, only randomized controlled trials (RCTs), and comparative meta-analysis studies published in the English language, published in the last ten years (2013-2022) and whole full literature available were included. Theses, conference abstracts, reviews, non-English studies, and studies whose data were unreliable for extraction and analysis were all excluded.

PICO		
	Inclusion Criteria	***Exclusion Criteria***
Population	Diabetic patients aged >18 years	Diabetic patients aged <18 years
		Other types of diabetes include: T1DM, Secondary cause of diabetes, MODY, LADA, GDM
Intervention	SGLT2 inhibitors or GLP-1 agonists	Other OHGAs
Comparison	Placebo	
Outcome	Renal Outcome	Non-renal outcomes

Study Selection: Studies were selected following two distinct phases of eligibility; first the screening of titles and abstracts was done, and second the full-text screening was performed.

Data extraction: An offline standardized data extraction sheet was prepared to document the critical information related to the variables of interest including; (1) Study characteristics (e.g., author, year of publication, study design) (2) participant characteristics (e.g., sample size, age, baseline renal function) (3) intervention details (e.g., types of SGLT2 inhibitors and GLP-1 RA) (4) risk of bias domains; and (5) outcomes of interest (e.g., changes in eGFR, albuminuria levels, adverse renal events) from the selected studies.

Risk of bias assessment: After adopting the inclusive inquiry approach, the results of our database search yielded 2093 articles, of which 2012 were excluded. Finally, 81 articles were included for review in this study. Of these, 18 were RCTs, 22 were comparing Meta-analysis and 41 were individual Meta-analysis. The AMSTAR checklist (A Measurement Tool to Assess Systematic Reviews) and Cochrane Risk of Bias tool were used for the critical appraisal of selected articles to ensure that the selected meta-analyses were conducted using robust methods and provided reliable and valid conclusions. Additionally, the Cochrane Risk of Bias tool was utilized to assess the quality and risk of bias in the individual randomized controlled trials (RCTs).

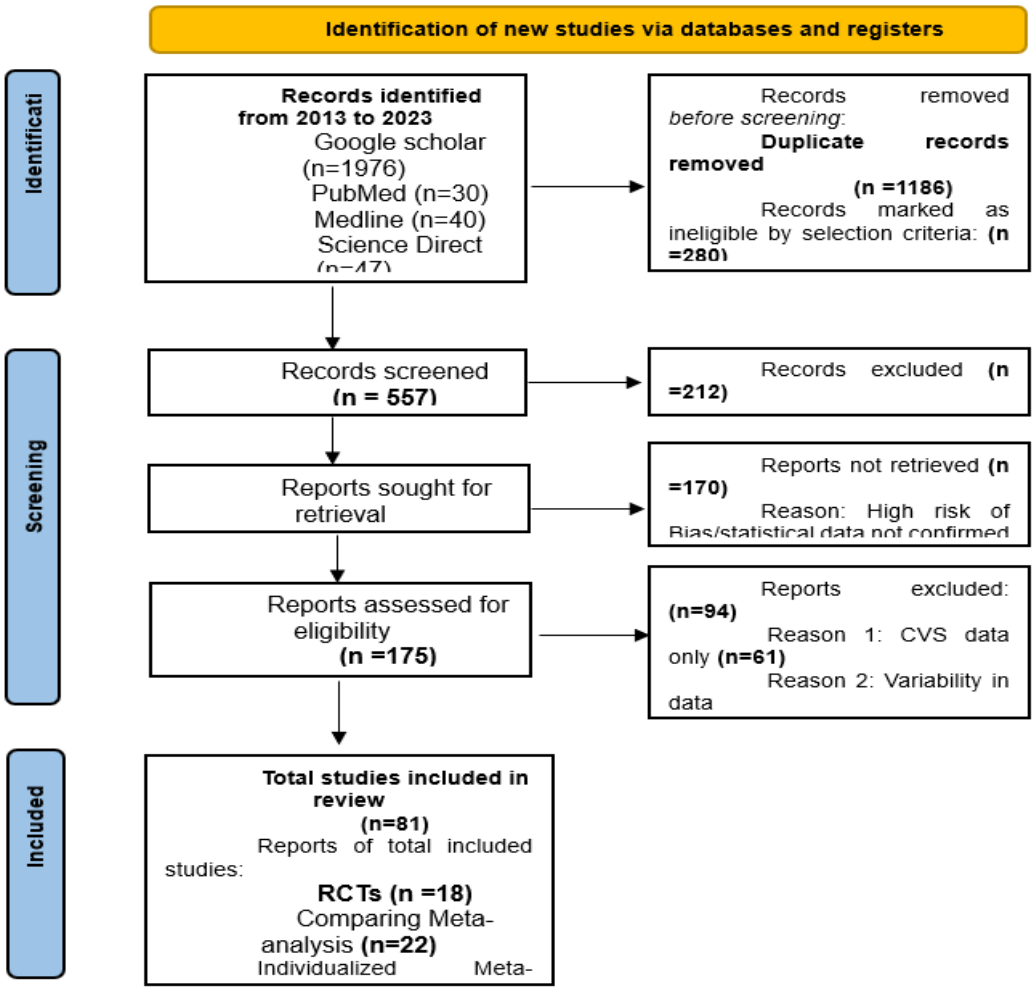

Figure 5: PRISMA Flow diagram

RESULTS AND DISCUSSION

In total, the data of 122540 patients from 18 RCTs with mean age ranging from 62-72 years. The follow-up period ranging from 2.4 to 4.2 years for SGLT2 inhibitors and 1 to 5.4 years for GLP-1 RA were included. Details of RCT trials and Meta-Analysis are presented in Table I, and II.

SGLT2 INHIBITORS

Effects of Different Drugs with Corresponding Trials and Kidney Protective Results

The difference between the baseline eGFR and UACR influences the results in almost all RCTs for SGLT2 inhibitors. The DAPA-CKD AND EMPA-KIDNEY trials had the lowest mean baseline eGFR (43 and 37.5 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) compared with DECLARE-TIMI 58, CANVAS, and EMPA-REG OUTCOME (85.2, 76.5, and 74 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, respectively). Conversely, CREDENCE had the highest level of macro-albuminuria (> 300 mg/g) followed by DAPA-CKD, compared with the median UACR of 8 and 7 mg/g for CANVAS and DECLARE-TIMI 58, proportionately. Therefore, the DAPA-CKD AND EMPA-KIDNEY population had the most baseline kidney disease risk in comparison to other SGLT2i RCTs, in contrast, DECLARE-TIMI 58 and CANVAS had the lowest risk of kidney disease with respect to the eGFR and UACR. (Kluger *et al*., 2019). This diversity of established CKD with or without DM in selecting patients resulted in a wide range of outcomes. Most of these trials mentioned above included participants with normal to mild kidney disease, only the two trials CREDENCE and DAPA-CKD exclusively included patients with moderate to severe kidney disease with macroalbuminuria. The percentage of patients with eGFR < 60 mL/min/1.73 m2 ranged from 7.4% in DECLARE-TIMI 58 trial to 59.8% in CREDENCE. While, DAPA-CKD (empagliflozin) claims a 50 % reduction in sustained eGFR deterioration and other kidney

parameters, almost all the other major trials like EMPA-REG, EMPA-CKD, and CANVAS reported more than a 40% reduction in eGFR declination. Overall, the CREDENCE trial affirms KCO decrease by 34% and ESKD by 32% (Perkovic, V et al., 2019). In addition, CANVAS trials state microalbuminuria declined by 20% and macroalbuminuria by 42%, while the mean ACR reduced by 18%. EMPA-REG Outcome trial also asserts a reduction of macroalbuminuria by 38%. The SGLT2 inhibitors significantly reduced albuminuria levels across all ranges, interesting SGLT2 inhibitors benefited macroalbuminuria (HR 0.82 [0.65-1.04]) more than the Normal (HR 091 [0.80-1.02]), and microalbuminuria (HR 0.99 [0.84-1.16]) (McGuire, Darren *et al*., 2020).

GLP-1 RA

Effects of Different Drugs with Corresponding Trials and Kidney Protective Results

In all major trials like LEADER (Liraglutide) and SUSTAIN-6 trials (semaglutide) and others reported that compared to placebo, drug-treated patients experienced a little but significant reduction in the composite kidney outcome, primarily benefits obtained by the reduction in onset of macroalbuminuria. SUSTAIN -6 and AMPLITUDE-0 showed a significant reduction in eGFR (HR, 0.64 [95% CI, 0.75–0.99]), and (HR, 0.68 [95% CI, 0.57–0.91]) respectively. Contrary, to the GLP-1 trials illustrating a non-significant decrease in eGFR compared to placebo. (HR, 0.86 [95% CI, 0.74–1.03]). The AWARD 7 trial better explains eGFR mean reduction (-3.3 versus −0.7 ml/min/1.73 m^2). The kidney benefit effect is mainly due to a reduction in albuminuria. ELIXA trial notifies that on average 21%, and 29% reduction in microalbuminuria, and macroalbuminuria respectively. SUSTAIN 6 trial claims that the treatment group showed a reduction in 46% of the progression of albuminuria in participants ((HR, 0.54 [95% CI, 0.37–0.77]). LEADER, REWIND, and AWARD-7 all showed approximately 21 % to 26% reduction of albuminuria versus placebo (95% CI, 20%-27%). (Mann *et al*., 2017). We in this narrative review declare that the mean decreases in pre-specified kidney composite outcome by an average of 19 % (HR, 0.81 [95% CI, 0.74–1.03]).

META-ANALYSES COMPARING SGLT2I VERSUS GLP-1 RAS RENAL OUTCOMES

In general, both SGLT2i and GLP1-RA reduce kidney disease progression and macroalbuminuria progression, but only SGLT2i reduces eGFR, ESRD, or renal death. The most recent and one of the largest trials in terms of participants (N= 209, 754) (Shi, Q et al., 2023) assert that SGLT2i and GLP-1RA are superior to other anti-diabetic drugs in terms of CV risk reduction, but SGLT2i is superior in reducing renal outcomes [(OR 0.61 (0.55-0.67)] versus GLP-1 RA [OR 0.83 (0.75-0.92)]. Zelniket, TA (2019) also concluded in his meta-analysis of eight RCTs that both SGLT2i [(HR, 0.62; 95% CI, 0.58-0.67)] and GLP1-RA [(HR, 0.82; 95% CI, 0.75-0.89)] decreased the kidney disease progression including macroalbuminuria, but only SGLT2i reduced the risk of worsening eGFR, end-stage kidney disease, or renal death [(HR, 0.55; 95% CI, 0.48-0.64)].

A systematic review and meta-analysis by Wei, XB (2021), comparing CV, mortality, and renal outcomes in T2DM advocates that SGLT2 significantly reduced KCO [HR; 0.62 (0.54-0.69)] versus GLP-1 RA [HR; 0.84 (0.75-1.02)]. Different drugs in both groups have different efficacy for preventing different cardiorenal endpoints. Another systematic review of nine studies (81,206 patients) included patients with/without albuminuria declared that, compared to GLP-1 RAs, SGLT-2 inhibitors were linked to a considerably decreased relative risk of renal adverse outcomes in both patients with and without albuminuria (RR 0.75 [95% CI 0.63-0.89] and (RR 0.59 [95% CI 0.44-0.79], respectively).(Kawai *et al*., 2022). The sensitive data analysis of a meta-analysis of thirteen studies (N=32,949 participants) surmises that SGLT-2 inhibitors bring a reduction in overall renal events by 32 % [RR 0.68 [0.59-0.78]. However, GLP-1 RAs did not noticeably decrease renal adverse events [0.86 [0.72-1.03]. (Yamada *et al*., 2021).

Compared with placebo the use of SGLT2i showed significant reductions (36%) [RR 0.64 (0.54-0.75)], whereas GLP-1RAs were associated with kidney composite outcome (18%) [RR 0.82 (0.70-0.92)] (Giugliano *et al*., 2022). A meta-analysis of 16 trials (Cao *et al*., 2022) denounces that SGLT2 inhibitors decrease KCO by 36% compared to GLP-1 RA by 14%. Similar results were plotted by

(Lin *et al*., 2021). Most of the meta-analyses only outline renal outcomes in detail but (Zhang, Y et al., 2022) also compared drug's effectiveness in terms of KCO in same class with high certainty. The study claims that the most effective drugs are SGLT2 inhibitors (Dapagliflozin> Empagliflozin>Canagliflozin) and the least effective are all from the GLP-1 RA group (Liraglutide>Dulaglutide>Exenatide). Similar results are also found in another meta-analysis (Alhassane Diallo *et al*., 2022).

In one study 2551 participants in each group of SGLT2i and GLP-1RA with a mean age of 56·2 years, and mean eGFR 78·0 mL/min/1·73m ^{2} with 12% having macro-albuminuria were examined. After 1.1 years of follow-up, SGLT2i users had a KCO of [(HR=0·77, 95%CI 0·62–0·96)] versus GLP-1 RAs (HR 0.89 [95% Cl 0.75-1.05]) mainly because of a decrease in ESKD, slow eGFR decline (1.19 Vs. 1.95 mL/min/1·73m ^{2}), and ↓ macroalbuminuria. Furthermore, the benefits of SGLT2i did not alter by age, sex, baseline eGFR/albuminuria status, hemoglobin A1C (HbA1c), and RAS inhibitor use (Lui *et al*., 2022). The other study was done in a very small Japanese population, claiming that yearly eGFR decline for SGLT2 inhibitors was (-1.8 [95 %CI, -2.7, -0.9] and for GLP-1 RA was - 3.4 [95 %CI, -4.6, -2.2]. Also, the new onset of KCO was significantly lower in SGLT2i-treated patients (11%) versus GLP1Ra-treated (27%). (Kobayashi *et al*., 2022).

Generally, the use of SGLT2 inhibitors resulted in a 34% to 45% reduction in kidney adverse outcomes, while GLP1-RA treatment reduced the risk by approximately 17% to 21%. These findings highlight the renoprotective effects of both drug classes, with SGLT2 inhibitors demonstrating a moderately greater impact on reducing kidney adverse outcomes. Furthermore, this analysis assessed the progression of eGFR deterioration as indicated by doubling of serum creatinine (S/Cr), the need for transplant treatment therapy, and/or progression to ESRD, the data indicated that SGLT2 inhibitors led to a 34% to 40% improvement in all of these parameters. In contrast, GLP1-RA treatment led to a comparatively smaller reduction of approximately 15% to 19% in pre-defined primary kidney outcomes compared to placebo, suggesting a lack of direct impact on kidney function in this regard.

In terms of the progression to macroalbuminuria, both SGLT2 inhibitors and GLP1-RA demonstrated a beneficial effect. The use of SGLT2 inhibitors reduced the risk of progression to macroalbuminuria by 38% to 42%, while GLP1-RA treatment resulted in a reduction of approximately 10% to 29%. These findings highlight the potential of both drug classes to mitigate the development and progression of macroalbuminuria in patients with T2DM. These pronouncements suggest that SGLT2 inhibitors may have a more pronounced effect in slowing down the decline in kidney function compared to GLP1-RA treatment.

SGLT-2 inhibitors blocked glucose reabsorption in the renal tubule, therefore the drug effect should be eGFR dependent. Even so, many meta-analyses of clinical trials revealed similar beneficial effects of SGLT-2 inhibitors in both eGFR 30-44 ml/min/1.73 m^2 and 45–59 ml/min/1.73 m^2 groups. (Petrykiv *et al*., 2017). Studies also revealed that SGLT-2 inhibitors decrease body weight, BP, and albuminuria regardless of eGFR, although glucose-lowering effects decreased as eGFR declined. (Heerspink *et al*., 2020).

Regarding GLP-1 RAs, our study did not find a significant difference between GLP-1 RAs and placebo, even though the hazard ratio is betwixt 0.81 to 0.88 in most of the meta-analyses. This conclusion is supported by the meta-analysis by (Kristensen *et al*., 2019) which also revealed that GLP-1 RAs were not associated with a significantly reduced risk of composite renal outcome. GLP1-RA has been reported to decrease kidney events mainly through a decline in macroalbuminuria (Mann *et al*., 2017). If macroalbuminuria is eliminated then GLP-1 has a non-significant effect size on KCO (HR, 0.92; 95% CI, 0.80–1.06) (Zelniker *et al*., 2019).

A sensitivity data analysis yielded that Kidney composite outcomes with SGLT2 inhibitors ranged from 34% to 45% (HR, 0.62; 95% CI, 0.58–0.67) with low heterogeneity (P<0.001), on the other hand, GLP1-RA reduced the relative risk of the broad composite kidney outcome (mainly through reduction in albuminuria) by 18% (HR, 0.82; 95% CI, 0.75–0.89) with heterogeneity of (P<0.001). Furthermore, other components of kidney disease like doubling of serum creatinine, and ESRD also varied between the two drugs by almost the same percentage difference. (Wei XB *et al*., 2021).

Conclusion

The main outcomes assessed in this narrative review were advancements in assessed glomerular filtration percentage, diminutions in urinary albumin amounts, and adverse kidney happenings. The analyses showed a steady improvement following treatment with SGLT2 inhibitors. Although the analytical results diverged, most studies unveiled an enhancement ranging from modest to substantial boots in eGFR with SGLT2i therapy.

In most of the studies, the results consistently demonstrated a significant decrease in albuminuria levels with SGLT2 inhibitors therapy, indicating improved renal function. A reduction in albuminuria was observed across all levels of initial albumin excretion.

Furthermore, the extent of albuminuria reduction is dose-dependent, suggesting that higher dosages of SGLT2 inhibitors may result in greater improvements in renal function.

To conclude, all RCTs and meta-analyses published to date unanimously highlighted the renoprotective effects of SGLT2 inhibitors, evidenced by the consistent reduction in albuminuria levels and improvement in eGFR observed across the studies. Moreover, the renoprotective effect of SGLT2 inhibitors equally safeguards non-diabetic kidney disease.

On the other hand, GLP-1 RAs consistently reduce the progression of albuminuria, but their impact on changes in eGFR or composite kidney adverse outcomes in T2DM is not consistently reported.

The interpretation of both drug class effect sizes is limited by many factors including heterogeneity, randomization, basic participant's characteristics, and many more, which may raise concerns about the reliability of these trial results. However, more, recent and ongoing studies are placing greater emphasis on and showing consistency in renal outcomes. These studies are highly relevant to the future treatment and diabetic kidney prevention in T2DM.

Overall, both classes are recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as first-line therapy in patients with T2DM and established ASCVD or multiple ASCVD risk factors to reduce the risk of major adverse cardiovascular events (MACE), and adverse kidney outcome regardless of baseline HbA1c levels (ADA.2021).

The comprehensive evaluation of selected studies' outcomes provides compelling evidence of the renoprotective potential of SGLT2 inhibitors, instilling hope for improved long-term kidney health in individuals with type 2 diabetes mellitus.

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