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GLOBAL JOURNAL OF
Obesity, Diabetes and Metabolic Syndrome

ISSN: 2455-8583 DOI: https://dx.doi.org/10.17352/gjodms

Review Article

Brief Review of Newer Antiglycemic Agents as Options in the Treatment of Diabetic Kidney Disease

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Received: 17 Ferbruary, 2020
Accepted: 09 May, 2020
Published: 11 May, 2020

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Keywords: Diabetes; kidney disease; DPP4: Dipeptidyl peptidase 4; GLP1: Glucagon-like peptide 1, SGLT 2: Sodium glucose co-transporter 2

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Abstract

Diabetes remains the leading cause of chronic kidney disease and with its increased prevalence the risk for Diabetic Kidney Disease (DKD) continues to rise and has a significant impact on diabetes morbidity and mortality as well as health care resources. There is a clear need to clinicians and patients for new treatments to limit the burden of DKD. Three classes of non-insulin therapy for type 2 diabetes mellitus (T2DM), dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP1) agonists, and sodium glucose co-transporter 2 (SGLT2) inhibitors have been evaluated in large cardiovascular safety studies in which exploratory or post-hoc analyses shed some light on renal outcomes with these agents. Smaller studies focused on efficacy and safety in patients with T2DM and diabetic kidney disease also provide some evidence of renal outcomes. As a class, both DPP4 inhibitors and GLP1 agonists show promise in reducing albuminuria but have so far not been shown to impact more robust renal outcomes such as doubling of serum creatinine or progression in renal insufficiency. More compelling data exist on the benefits of SGLT2 inhibitors. From the cardiovascular safety studies, empagliflozin, canagliflozin, and dapagliflozin have shown reductions in not just albuminuria, but also show significant reductions in progression of renal insufficiency and a small reduction in the development of end-stage renal disease. The cardiovascular safety studies, however, were not designed to specifically assess renal benefit. Canagliflozin in a landmark trial specifically designed to evaluate its use in patients with diabetes and DKD, has shown to reduce doubling of serum creatinine, progression to end-stage renal disease while also demonstrating a reduction in cardiovascular morbidity as well. It is the first agent in nearly twenty years to obtain an indication for the treatment of DKD.

Abbreviations

CKD: Chronic Kidney Disease; T2DM: Type 2 Diabetes Mellitus; US: United States; DKD: Diabetic Kidney Disease; DPP4: Dipeptidyl Peptidase 4 inhibitors, glucagon-like peptide 1 agonists; FDA: Food and Drug Administration; CVOT: Cardiovascular Outcome Trial; UACR: Urine Albumin Creatinine Ration; eGFR: estimated Glomerular Filtration Rate; CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

Introduction

Diabetes continues to be the leading cause of Chronic Kidney Disease (CKD) worldwide with an estimated 40% of patients with diabetes going on to develop some degree of CKD [1]. This greatly increases the risk for end-stage renal disease

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and cardiovascular morbidity and mortality [2,3]. With the ever-increasing prevalence of diabetes, the incidence of CKD continues to rise as well. In older patients in particular, CKD rates increase with advanced age and in the United States (US) Medicare population, this increase resulted in an estimated $39 billion in health care expenditures in 2017 for patients with CKD and concurrent diabetes [4]. For the past two decades, leading US guidelines in the treatment of diabetes have stressed the need for improved glycemic and hypertension control as a means to limit the onset of diabetic kidney disease (DKD) or to reduce its progressive nature [5]. Despite these recommendations there remains a significant residual risk for the onset or progression of DKD. Efforts have been called for to improve overall health outcomes for patients with DKD and for the development of new therapeutic entities that can stem this tide. [1,6]. This review assesses the renal benefits of three classes of antidiabetic agents. This includes agents that affect the incretin system, i.e. Dipeptidyl Peptidase 4 inhibitors (DPP4i) and Glucagon-Like Peptide (GLP)-1 agonists, or affect kidney glucosuria i.e. Sodium Glucose co-Transporter 2 inhibitors (SGLT2). These three classes are highlighted due to the fact there is renal data, positive or neutral, with each agent from glycemic efficacy studies, in patients with or without existing DKD, and each agent within these classes has undergone a Food and Drug Administration (FDA)-mandated Cardiovascular Outcome Trial (CVOT). These CVOT studies are typically much larger and most included a prespecified evaluation of a composite renal outcome or post-hoc analysis of such. Lastly, one landmark study specifically designed to evaluate an agent in patients with DKD showing robust benefit in this patient population will be discussed. It is the intent of this brief review to provide the reader with synopses of each class and if or where the agents may play a role in treating DKD.

Incretin agents

DPP4 inhibitors

In studies designed to assess glycemic efficacy in patients with or without existing DKD, the DPP4i data has shown this class of agents likely has a positive effect on reducing albuminuria via changes in Urine Albumin-to-Creatinine Ratio (UACR). These trials differ in duration of therapy, extent of baseline DKD, and how changes in DKD were reported. The changes in UACR vary from baseline by 5-43 mg/g depending on study and agent evaluated [7-9]. The studies to date, however, have not shown a significant reduction in progression of more robust renal outcomes such as doubling of serum creatinine, progression to end-stage renal disease, or renal death. The CVOT studies involving the DPP4is each included a composite renal outcome. It should be noted the CVOT studies mandated by the FDA are to demonstrate cardiovascular safety compared to placebo and are not specifically designed to evaluate renal outcomes. Subjects evaluated in these studies tended to be older with established cardiovascular disease or at high risk for such and baseline renal function and degree of albuminuria varied between study. None of the studies showed a statistically significant or clinically relevant reduction in progression of renal insufficiency, need for dialysis, or renal death [10-13]. Currently, none of the agents within this class are approved for use in DKD and based on the limited data described above should not be used off-label for such.

GLP1 agonists

The data for GLP1 agonists in studies evaluating glycemic benefit in patients with T2DM with or without existing DKD show mixed results in UACR improvements or changes in renal function. Three agents within this class, liraglutide, dulaglutide, and oral semaglutide have each assessed renal outcomes in patients with T2DM and moderate renal impairment (baseline estimated glomerular filtration rate (eGFR) between 30 and 59 ml/min/1.73m^2). In a six-month study of over 300 patients no changes in UACR or improvement in eGFR were found in those receiving oral semaglutide compared to placebo [14]. A twelve-month study comparing dulaglutide to insulin glargine in over 570 patients showed a modest improvement in eGFR with dulaglutide (<3 ml/min/1.73m^2) compared to those receiving insulin therapy but failed to show a difference in UACR between the two groups [15]. Liraglutide failed to show a change in either albuminuria or change in eGFR compared to placebo in a six-month study in over 270 patients [16]. Renal outcomes in the much larger CVOT studies were evaluated for many of the agents within this class including lixisenatide, liraglutide and once-weekly formulations of semaglutide, dulaglutide, and exenatide (Table 1). Each study varied in baseline cardiovascular risk and duration of study. The average baseline renal function was greater than 70 ml/min/1.73m^2 and how baseline UACR was expressed varied widely between study but most patients had normal albuminuria. Lixisenatide and oral semaglutide did not have a prespecified composite renal outcome embedded in their respective CVOT studies. However, lixisenatide showed a smaller percent change in UACR over the two-year study compared to placebo but did not show an improvement in the development of persistent macroalbuminuria (>300 mg/g), change in eGFR, or in doubling of serum creatinine [17]. In contrast to the CVOT studies with DPP4is, the studies with the GLP1 agonists that included a composite renal outcome each showed a significant 15-36% relative reduction though the composite outcome differed between studies (Table 1). [18-21] However, upon closer evaluation, it appears that the driving force behind the reduction in the composite outcome was change in albuminuria and no study showed an ability to slow the progression of eGFR decline or need for renal replacement therapy. Currently, none of the agents within this class are approved for use in DKD and based on the limited data described above should not be used off-label for such.

SGLT2 Inhibitors

Studies evaluating glycemic efficacy in patients with and without baseline DKD show that the SGLT2 inhibitors also improve albuminuria. Empagliflozin in patients with microalbuminuria (UACR 30-300 mg/g) has demonstrated a 32% reduction in UACR and a 41% reduction in those with baseline macroalbuminuria (>300 mg/d) [22]. Ertugliflozin has also shown a 29-33% reduction in UACR in a 24-month study compared to subjects receiving placebo or glimepiride [23]. Canagliflozin in greater than 260 patients with stage 3

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Table 1: Renal Outcomes from Cardiovascular Outcome Trials of Injectable GLP1 agonists or Oral SGLT-2 inhibitors.

Agent Evaluated	Study Duration (years)	Number of Subjects	Composite Renal Outcome	Individual Renal Outcomes
GLP1 Agonists				
Lixisenatide [17]	2.1	6068	NA	% change in UACR +24% Lixisenatide vs +34% Placebo (p=0.004) Baseline UACR < 300 to ≥ 300 mg/g 6.5% Lixisenatide vs 7.7% Placebo (NS) Doubling of serum creatinine 1% Lixisenatide vs 1% Placebo (NS) Development of ESRD: < 1% in each group (NS)
Liraglutide [18]	3.8	9340	New-onset persistent macroalbuminuria, doubling of serum Cr and eGFR < 45 ml/min/1.73 m2, need for renal replacement, or renal death 15.0 Liraglutide vs 19.0 Placebo (rate per 1000 patient years of observation), 22% relative reduction (p=0.003)	Rate per 1000 patient years of observation Persistent macroalbuminuria 9.0 Liraglutide vs 12.1 Placebo, 26% relative reduction (p=0.004) Doubling of serum Cr and persistent eGFR < 45 ml/min/1.73 m^2 4.9 Liraglutide vs 5.5 Placebo (NS) Need for renal replacement therapy 3.1 Liraglutide vs 3.6 Placebo (NS) Renal death 0.4 Liraglutide vs 0.3 Placebo (NS)
Semaglutide (once weekly subcutaneous) [19]	2.1	3297	New or worsening nephropathy (macroalbuminuria, doubling of serum Cr and CrCl < 45 ml/min/1.73 m^2, or need for renal replacement therapy) 3.8% Semaglutide vs 6.1% Placebo, 36% relative reduction (p=0.005)	Persistent macroalbuminuria 2.7% Semaglutide vs 4.9% Placebo, 46% relative reduction (p=0.001) Doubling of serum Cr and persistent CrCL < 45 ml/min/1.73 m^2 1.1% Semaglutide vs 0.8% Placebo (NS) Need for renal replacement therapy 0.7% Semaglutide vs 0.7% Placebo (NS)
Exenatide [21]	3.2	14752	Composite 1: First event of a 40% decline in eGFR, renal replacement, or renal death 3.8% Exenatide vs 4.2% Placebo (NS) Composite 2: Composite 1 plus incident macroalbuminuria 5.8% Exenatide vs 6.5% Placebo, 15% relative reduction (p=0.03)	New macroalbuminuria 2.2% Exenatide vs 2.5% (NS) Mean change in eGFR 0.21 ml/min/1.73 m^2 (NS)
Dulaglutide [20]	5.4	9901	New macroalbuminuria, sustained decline in eGFR ≥30% from baseline, or need for renal replacement 17.1% Dulaglutide vs 19.6% Placebo, 15% relative reduction (p=0.0004)	New macroalbuminuria 8.9% Dulaglutide vs 11.3% Placebo, 23% relative reduction (p<0.0001) Sustained decline in eGFR ≥30% 9.2% Dulaglutide vs 10.1% Placebo (NS) Need for renal replacement 0.3% Dulaglutide vs 0.4% Placebo (NS)
SGLT2 inhibitor				
Empagliflozin [26]	2.6	7020	Progression to UACR > 300 mg/g, doubling of serum Cr and decline in eGFR ≤ 45 ml/min/1.73m^2, initiation of renal replacement, or renal death 12.7% Empagliflozin vs 18.8% Placebo, 39% relative reduction (p<0.001)	Progression to UACR > 300 mg/g 11.2% Empagliflozin vs 16.2% Placebo, 38% relative reduction (p<0.001) Doubling of serum Cr and decline in eGFR ≤ 45 ml/min/1.73 m^2 1.5% Empagliflozin vs 2.6% Placebo, 44% relative reduction (p<0.001) Initiation of renal replacement therapy 0.3% Empagliflozin vs 0.6% Placebo, 55% relative reduction (p=0.04)

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Canagliflozin [27,28]	3.6	10142	40% reduction in eGFR, renal replacement initiation, or renal death 5.5 Canagliflozin vs 9.0 Placebo (rate per 1000 patient years), 40% relative reduction (p values not provided)	Rate per 1000 patient years (p values not reported but 95%CI did not include 1) Progression of albuminuria 89 Canagliflozin vs 128 Placebo, 27% relative reduction 40% reduction in eGFR 5.3 Canagliflozin vs 8.7 Placebo, 40% relative reduction Doubling of serum creatinine 1.2 Canagliflozin vs 2.4 Placebo, 50% relative reduction
Dapagliflozin [29]	4.2	17160	Sustained decrease of 40% or greater in eGFR and < 60 ml/min/1.73 m^2, new end-stage renal disease, or death due to cardiovascular or renal cause 4.3 Dapagliflozin vs 5.6 Placebo (rate per 1000 patient years), 24% relative reduction (p value not provided, 95%CI not including 1)	(p values not reported and/or 95%CI did not include 1 for relative reductions) Sustained decrease of 40% or greater in eGFR and < 60 ml/min/1.73 m^2, new end-stage renal disease, or death due to renal cause 1.5 Dapagliflozin vs 2.8 Placebo, (rate per 1000 patient years), 47% relative reduction Sustained 40+% decrease in eGFR and eGFR < 60 ml/min/1.73 m^2 1.4% Dapagliflozin vs 2.6% Placebo, 46% relative risk reduction End-stage renal disease 0.1% Dapagliflozin vs 0.2% Placebo, 69% relative reduction

GLP: Glucagon-Like Peptide; SGLT: Sodium Glucose co-Transporter; NA: Not Available or Not Assessed; UACR: Urine Albumin; creatinine ratio; NS: Not Significant; ESRD: End-Stage Renal Disease; Cr: Creatinine; eGFR: estimated Glomerular Filtration Rate; CrCl: Creatinine clearance, CI: Confidence Interval

CKD demonstrated a 21-30% reduction in UACR compared to placebo in a six-month study [24]. Lastly, dapagliflozin in 166 patients with diabetes, DKD, and baseline microalbuminuria showed a 44-57% reduction in UACR compared to placebo [25]. The argument for use of this class of agent to stem progression of DKD gets more compelling upon assessment of composite renal outcomes from the three published CVOT studies involving empagliflozin, canagliflozin, and dapagliflozin [26-29]. (Table 1) As in the CVOT studies involving GLP1 agonists, in the SGLT2 inhibitor CVOT studies the majority of patients had normal baseline albuminuria and renal function and the studies varied in duration, size, and baseline cardiovascular risk. A 24%-40% relative reduction in the composite renal outcomes were found in these three studies and in the case of both canagliflozin and dapagliflozin the composite outcome did not include changes in UACR suggesting albuminuria is not the driving force in these outcomes [26-29]. Each study when looking at changes in renal function showed a significant reduction in slowing decline in eGFR and in the case of both empagliflozin and dapagliflozin these two studies found a significant, albeit small, reduction in those requiring renal replacement therapy or progressing to end-stage renal disease. Despite the CVOT studies not being specifically designed to show renal benefit, each showed more robust renal outcomes than the other two classes discussed above.

In 2019, the landmark Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study was published and to date serves as the most compelling evidence in improving renal outcomes with a SLGT2 inhibitor in patients with T2DM and DKD [30]. The 2.6-year study evaluated low dose (100 mg daily) canagliflozin compared to placebo in patients with diabetes whose baseline eGFR was between 30-89 ml/min/1.73m^2 (mean 56) and UACR between 300-5000 mg/g (mean 927). The study found a 30% relative reduction in the primary renal outcome (defined as need for dialysis, renal transplantation, sustained eGFR <15 ml/min/1.73m^2, doubling of serum creatinine, or death from renal or cardiovascular disease). Components of the primary outcome assessed separately showed significant reductions in progression to end-stage renal disease, a doubling of serum creatinine, and reductions in cardiovascular events and heart failure admissions. The specific mechanisms of how these agents improve renal outcomes is not fully understood but is likely multifactorial and can't be explained by mild improvements in glycemic (-0.11%) or systolic blood pressure (-2.4 mm Hg) control seen in the CREDENCE study [30,31]. Canagliflozin now has a new indication from the FDA to reduce DKD in patients with T2DM, the first such indication for an agent in nearly 20 years. In addition to standards of care to improve glycemic, blood pressure control, and use of agents to block the renin angiotensin system, canagliflozin should be considered in patients who have similar baseline DKD as in the CREDENCE study.

Conclusions

While patients receiving a DPP4i or GLP1 agonist may experience improvements in albuminuria, there is little data to support their use to slow the progression of DKD in terms of more robust renal outcomes that show a slowing of disease progression related to renal function or need for renal replacement therapy. The SGLT2 inhibitors, on the other hand, in their CVOT studies and canagliflozin in the CREDENCE study show this class of agents does influence these types of renal outcomes. Whether the results found in CREDENCE

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will also hold true for the other agents in this class remains to be determined but both dapagliflozin and empagliflozin have ongoing studies evaluating this concept. New research opportunities exist to assess if SGLT2 inhibitors have a positive effect on treating patients with Type 1 diabetes and DKD or in patients with CKD not due to diabetes. Clinicians should stay abreast of any new published studies in DKD with any of these class of agents.

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