J MEDICINE 2023; 24: 43-49

Review Article

Can DPP-4 Enhibitors and SGLT-2 Inhibitors Pleotropic Effects be Extended to Treat Diabetic Nephropathy?

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Abstract

Impaired insulin secretion and resistance remain the core defects in T2DM, but at least six other pathophysiological abnormalities contribute to the dysregulation of glucose metabolism. Diabetic nephropathy is one of the most common microvascular complications and a major cause of end-stage renal disease. Despite many treatment options available, diabetic kidney disease continues to affect a large population with diabetes. The kidneys have the highest DPP-4 expression level in mammalians. DPP-4 is expressed in several segments of the nephron and the tubule interstitium, placing it at the nexus of inflammation, immune system activation, glomerular and proximal tubular function, salt regulation, and kidney fibrosis. Moreover, DPP-4 expression and urinary activity are up-regulated in diabetic nephropathy, highlighting its role as a potential target to manage diabetic nephropathy. DPP-4 inhibition is associated with mitigation of diabetic and hypertensive renal injury and protection of renal function. Renal glucose reabsorption by SGLT proteins is a critical component of glycemic regulation. SGLT2 protein expression is increased in human diabetic nephropathy even with advanced kidney disease indicating that SGLT2 can be an effective target in treatment of diabetic nephropathy. This review article discusses roles played by DPP-4 inhibitors and SGLT-2 inhibitors alone and in combination in diabetic nephropathy supported by clinical evidences. MEDLINE and EMBASE were searched through September 2022. Randomized controlled trials published in English that evaluated SGLT2 inhibitors and/or DPP4 inhibitors in patients with T2DM were selected.

Keywords: *Type 2 diabetes mellitus, diabetic nephropathy, DPP-4 inhibitors, SGLT-2 inhibitors*

DOI: *https://doi.org/10.3329/jom.v24i1.64903*

Received: *10.09.2022;* ***Accepted:*** *12.11.2022.*

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease largely characterized by impaired insulin secretion and action. It is the most common and clinically important metabolic disorder which has become a global pandemic in recent decades and a major healthcare burden worldwide [1]. Prof Ralph DeFronzo proposed an "ominous octet" of eight factors that contribute to the pathophysiology of T2DM in 68th Scientific Sessions of American Diabetes Association: decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucose reabsorption, decreased glucose uptake, neurotransmitter dysfunction, increased hepatic glucose production, and increased glucagon secretion [2]. Individuals with T2DM are at high risk for both microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (cardiovascular comorbidities) [3].

Diabetic nephropathy (DN) is a major cause of end-stage renal disease and affects a large number of patients with diabetes. DN is characterized by albuminuria and morphological changes such as glomerular thickening, formation of nodular glomerulosclerosis, interstitial fibrosis and decreased endothelial cell fenestration. Besides, the involvement of renin-angiotensin-aldosterone system

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(RAAS), inflammation and genetic factors are the key pathways in the progression of DN [4]. Despite the great strides that have been made in the understanding and management of T2DM, insulin resistance and diabetes-related complications like diabetic nephropathy are increasing unabated as development of specific treatments for DN has not yet been identified [3].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are one of the newer types of oral glucose-lowering drug approved for type 2 diabetes, with the first-in-class sitagliptin approved in 2006 in the United States. DPP-4 inhibitors, also known as gliptins, are orally administered drugs with moderate glycemic efficacy and a low risk for hypoglycemia or weight gain [5]. DPP-4 inhibitors offer effective and well-tolerated treatment option for T2DM with any degree of renal impairment. Emerging evidence suggests that DPP-4 inhibitors used to treat type-2 diabetes may have nephroprotective effects. This kidney protection appears to be independent of glucose lowering and can potentially complement other therapies that preserve kidney function [6].

SGLT-2 inhibitors are a new class of anti-glycemic drugs that have been shown to lower blood glucose by inhibition of the sodium-glucose transporter 2 in the proximal tubule of the kidney and a concomitant increase in the urinary excretion of glucose (glycosuria). SGLT2 inhibitors are currently used primarily as anti-diabetic medications; however, their advantages go well beyond just blood glucose control. Multiple mechanisms contribute to the nephroprotective effects of SGLT-2 inhibitors in diabetic patients [7].

Epidemiology

About 537 million adults (20-79 years) worldwide have diabetes, the majority living in low-and middle-income countries, and 6.7 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. The total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045 [8]. Microvascular complications resulting from hyperglycemia, including kidney disease, are major clinical sequelae of type 2 diabetes. Consequently, approximately 50% of people with type 2 diabetes also have chronic kidney disease, making diabetes the leading cause of chronic kidney disease [5].

Pathophysiology

Despite optimal management, the risk of both microvascular and macrovascular complications has increased significantly, including diabetic kidney disease (DKD). DKD, an independent risk factor for coronary artery and peripheral vascular disease, is still a major contributor to morbidity and mortality of diabetic patients worldwide. Hyperglycemia triggers many mechanisms resulting in renal injury, oxidative and inflammatory stress, and eventually progressive loss of kidney function [9].

The pathogenesis of DKD is complex and involves both hemodynamic and non-hemodynamic mechanisms of kidney injury. The majority of patients with DKD develop elevated albumin excretion before exhibiting kidney function decline and ultimately end-stage kidney disease (ESKD). One of the earliest abnormalities detected in animals and humans' leading to DKD is therefore single-nephron hyperfiltration. Although the pathogenesis of hyperfiltration is not yet completely understood, changes in both afferent and efferent arteriolar tone have been strongly suggested. These hemodynamic changes have been correlated with increased intra-glomerular wall tension and shear stress, leading to activation of pro-inflammatory cytokines, albuminuria and progressive kidney disease [10].

Glomerular hyperfiltration is involved in the occurrence of diabetic kidney disease, and increased local angiotensin II (Ang II) induces constriction of efferent arteriole, thus causing changes of auto-regulation and glomerular hypertension. At the same time, hyperglycemia and compensatory hyperinsulinemia through reactive oxygen species (ROS) production promote vascular endothelial dysfunction, activation of protein kinase C (PKC) and advanced glycation end-products (AGEs)-mediated pro-inflammatory response. Activation of endothelin cells is essential for podocyte injury and renal fibrosis in diabetic kidneys [9].

Biology of DPP4 in the Kidney

DPP-4 belongs to a family of proteolytic enzymes that are widely expressed in several tissues where they exert different functions. In particular, the DPP-4 enzyme exists in two forms, a soluble form circulating in the blood and a membrane-bound one present in several cell types. In the kidney, DPP-4 is localized on glomerular visceral epithelial cells, brush border of the S1–S3 segments of the proximal tubule and on endothelial cells where it usually acts by preferentially cleaving peptide hormones containing alanine at position two or proline at the NH_2-terminus. Hence, DPP-4 inhibitors are expected to have a significant impact on renal physiology [11].

Comparison of DPP4 expression levels to other known genes in proximal tubules and other segments of the nephron show relative abundance of DPP-4 in various parts of the nephron is depicted in figure 1 [12]. Interestingly, renal DPP-4 activity was found to be significantly higher in patients with type 2 diabetes and albuminuria compared with non-albuminuric diabetic patients or healthy individuals [5].

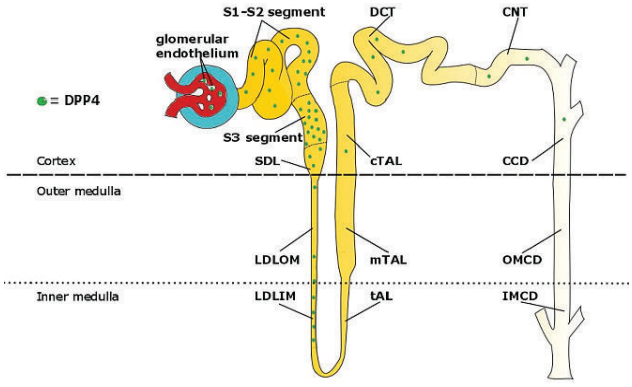

Figure 1. *DPP4 expression in the various segments of the nephron compared with other genes known to be highly expressed in the proximal tubule* [12].

S1–S3 segment, proximal tubules; SDL, short descending limb of the loop of Henle; LDLOM, long descending limb of the loop of Henle in the outer medulla;LDLIM, long descending limb of the loop of Henle in the inner medulla; tAL, thin ascending limb of the loop of Henle; mTAL, medullary thick ascending limb of the loop of Henle; cTAL, cortical thick ascending limb of the loop of Henle; DCT, distal convoluted tubule; CNT, connecting tubule; CCD, cortical collecting duct; OMCD, outer cortical collecting duct; IMCD, inner cortical collecting duct.

Role of DPP-4i in diabetic nephropathy

The functional significance of DPP-4 expression in non-proximal tubule portions of the nephron is currently unknown [12]. In the renal proximal tubule, however, it exerts more recognized actions. Firstly, its role is related to the sodium/proton exchanger isoform 3 (NHE3) activities in response to Ang II. Both Ang II inhibition and DPP-4 blockade result in reduced sodium absorption in the renal proximal tubule. It has also been observed, *in vitro* and *in vivo*, that DPP-4 inhibition restores megaline levels, reduced by the action of Ang II on renal proximal tubule. This would determine an increased uptake of albumin and other low-molecular-weight proteins [13].

In accordance with this, a physical interplay between DPP-4 and the NHE3 exchanger in the brush-border epithelium of the proximal renal tubule have been demonstrated, suggesting a functional relationship between them. This supports the involvement of DPP-4 enzyme in the NHE3-mediated reabsorption of sodium bicarbonate and water. DPP-4 inhibition might enhance natriuresis and diuresis in two ways: 1) by promoting down-regulation of NHE3 activity associated with GLP-1R activation and 2) by directly impairing NHE3 function due to the inhibition of DPP-4 [11].

It should also be considered that multiple peptide substrates other than GLP-1 are likely cleaved by DPP-4, thus suggesting that DPP-4 inhibition may affect the kidney physiology by other, non-incretin mediated pathways. For example, DPP-4 may target ANP, brain-derived natriuretic peptide (BNP), neuropeptide Y (NPY), peptide YY (PYY), and stromal-derived factor (SDF)-1á. Similar to ANP, BNP is known for its natriuretic and vasorelaxant effects. NPY stimulates vasoconstriction and up-regulation of sympathetic nerve activity whereas PYY mediates vasoconstriction only. SDF-1á plays an important role in protection of ischemically-injured tissues as well as in angiogenesis. DDP-4 inhibitors may therefore participate in the modulation of natriuresis, blood pressure, vascular function and tissue repair by augmenting endogenous levels of these peptides. The inhibition of NPY cleavage may also contribute to effect of gliptins on blood pressure as NPY is an agonist of Y1 receptor mediating peripheral vasoconstriction [11]. DPP-4, its substrates and DPP-4 inhibitors in diabetic nephropathy are summarized in figure 2 [14].

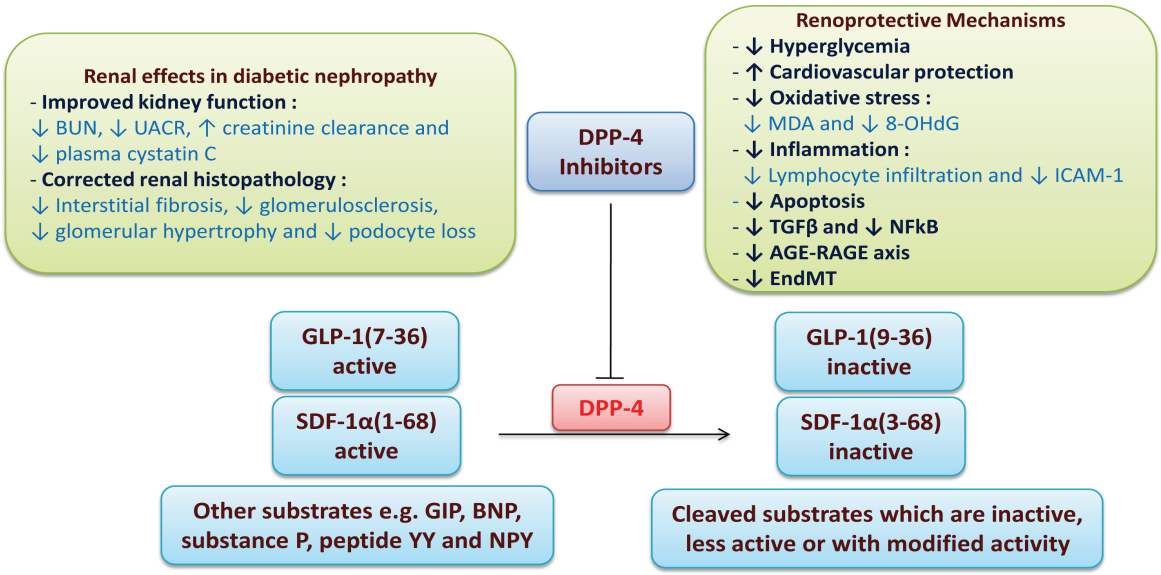

Figure 2. *DPP-4, its substrates and DPP-4 inhibitors in diabetic nephropathy* [14].

BUN, blood urea nitrogen; UACR, urinary albumin to creatinine ratio; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-22 -deoxyguanosine; ICAM-1, intercellular adhesion molecule-1; TGFâ, transforming growth factor beta; NFêB, nuclear factor kappa B; AGE, advanced glycation endproducts; RAGE, receptor of AGE; EndMT, endothelial-to-mesenchymal transition; GLP-1, glucagon like peptide-1; SDF-1a, stromal derived factor-1 alpha; GIP, glucose dependent insulinotropic polypeptide; BNP, brain natriuretic peptide; NPY, neuropeptide Y.

Clinical data on DPP-4 inhibitors in diabetic nephropathy

A few clinical studies have evaluated the renal effects of DPP-4 inhibitors in diabetic nephropathy. In an observational retrospective study on a cohort of T2DM patients, the nephroprotective effect of some DPP-4is (sitagliptin, linagliptin, saxagliptin, vildagliptin, and gemigliptin), in co-administration with other anti-diabetic drugs (especially metformin and sulfonylureas), was investigated evaluating albuminuria and estimated glomerular filtration rate (eGFR). Changes in the urinary albumin to creatinine ratio (UACR), eGFR, and metabolic parameters were compared before and after treatment. After a year, UACR was reduced by an average of 45 mg/g. Patients with macroalbuminuria had a significant decrease in proteinuria, whereas the effects on microalbuminuria were not statistically significant. Although eGFR did not change after one year of DPP-4 inhibitor treatment, reductions in eGFR were slowed in patients with microalbuminuria and reversed in macro-albuminuric or normo-albuminuric groups, four years after treatment. These studies support the evidence of a relevant DPP-4 influence on albuminuria in diabetic nephropathy [15].

Linagliptin in combination with RAAS inhibitors abolished UACR in type 2 diabetic patients with albuminuria after 24 weeks of treatment in a pooled analysis of four clinical studies. This effect was independent of the changes of HbA1c and systolic blood pressure [16].

CARMELINA study was a large, multicenter, randomized, placebo-controlled trial that involved T2 diabetes patients at high risk of cardiovascular events and with a high prevalence of CKD. This is the first to actively include patients with established CKD up to an eGFR <15 mL/min/1.73 m^2. The study aimed to assess cardioprotective and nephroprotective effects of linagliptin, added to usual anti-diabetic therapy. Linagliptin reduced albuminuria progression, but had no effect on other hard renal endpoints[17].

In the SAVOR-TIMI-53 trial, even in normoalbuminuric patients, the treatment with saxagliptin improved ACR, without any adverse effect on kidney function. Indeed, the favorable action of saxagliptin on albuminuria was not related to the improvement of glycemia. Anyway, despite lowering albumin excretion, no difference was found in ESRD incidence or in the progression of renal injury between saxagliptin and placebo [18].

In the EXAMINE trial which selected a specific diabetic population included 29% subjects with renal impairment having eGFR < 60 ml/min/1.73 m^2. Progression to dialysis was noted in 0.9% of subjects on alogliptin versus 0.8% of those receiving placebo [19].

Sitagliptin in DKD

The first observation of a positive effect of DPP-4 inhibitors on albuminuria in clinical settings has been made in a small trial by *Hattori et al*. in 37 non-CKD diabetic patients in which sitagliptin administered at a 50 mg dose was able to reduce albumin-to-creatinine ratio (ACR) compared to placebo [20].

Similarly, *Mori et al*. obtained a noteworthy albuminuria reduction in T2DM patients after six months of treatment with sitagliptin compared with other anti-diabetic agents [21].

More specifically, *Kawasaki et al*. investigated the action of sitagliptin on albuminuria in 247 T2D patients in an observational trial. They found that the ACR reduction was linked with the antihypertensive effect of sitagliptin. Therefore, authors concluded that sitagliptin exerts an anti-proteinuric effect through impacting on both blood pressure and eGFR [22].

Moreover, *Fujita et al*. and coworkers performed a cross-over study to investigate the effects of sitagliptin and alogliptin in twelve patients, with diabetic nephropathy, taking ARBs. The treatment regimen consists of three periods; sitagliptin for 4 weeks, alogliptin for 4 weeks and again sitagliptin for 4 weeks. The switch from sitagliptin to alogliptin, a stronger DPP-4 inhibitor, was associated with declined UACR and oxidative stress and elevated urinary cAMP and plasma SDF-1á [23].

Goldshtein et al. and coworkers compared the change in UACR in type 2 diabetic patients with albuminuria receiving sitagliptin to those receiving sulphonylurea as add-on to metformin monotherapy. Both sitagliptin and sulphonylurea decreased albuminuria as an add-on therapy to metformin, however, sitagliptin resulted in greater reductions in albuminuria independent of glycemic control compared to sulphonylurea [24].

TECOS trial confirmed the safety of Sitagliptin in patients with type 2 diabetes and cardiovascular disease. The study

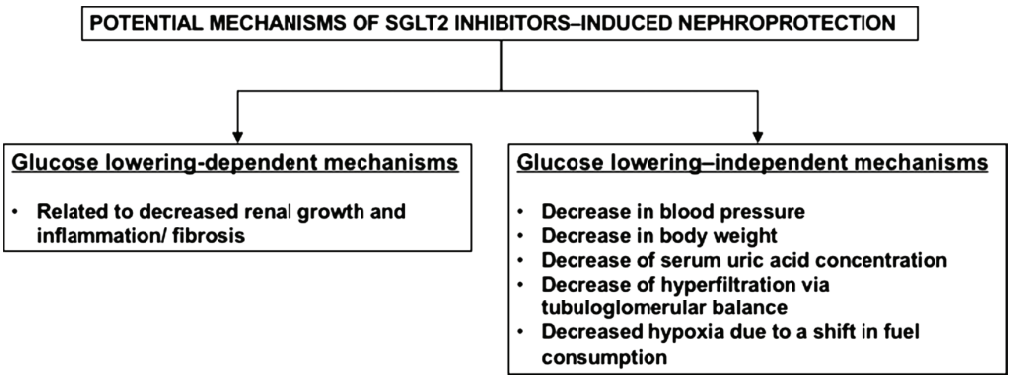

Figure 3. *Potential mechanisms of SGLT2 inhibitors-induced renoprotection [29].*

included a significant proportion of subjects with renal impairment (about 23% with eGFR < 60 ml/min/1.73 m^2). Post hoc analysis of the study showed that the presence of CKD strongly increased the risk of serious adverse events during follow-up, but the use of sitagliptin did not further increase this risk [25]. All these clinical studies lend support to the hypothesis that DPP-4is might exert nephroprotective effects.

Biology of SGLT-2 in the Kidney

The kidney reabsorbs all of the filtered glucose under normal physiological conditions. This occurs by means of two different transporters, namely SGLT1 and SGLT2. The density of SGLT-1 is higher in the distal third (S3 segment) of the proximal convoluted tubule of the nephron. Physiologically speaking, it plays a minor role in the reabsorption of glucose (10%). SGLT-2, on the other hand, is densely located in the proximal third (S1 segment) of the proximal convoluted tubule, especially in the renal cortex, and plays a major role in reabsorption of glucose (90%). These co-transporters are located on the luminal epithelium and are secondary active as they depend on Na^+- K^+ ATPase activity in the basolateral membrane for the active removal of sodium [26].

There is increasing evidence that renal proximal tubular glucose absorption is increased in humans and animal models of diabetes mellitus. Also, SGLT-2 mRNA and protein expression are increased in kidney biopsies from human subjects with diabetic nephropathy. In contrast, there is no change in SGLT-1 mRNA abundance. This finding was confirmed by immune-histochemical (IHC) analysis of SGLT-2 protein expression, which showed increased apical border staining of proximal tubule epithelium of diabetics, in contrast to weaker staining in the same pattern in normal kidneys [27].

Role of SGLT-2i in diabetic nephropathy

SGLT-2 inhibitors prevent both renal damage and the onset of chronic kidney disease in addition to their glucose-lowering effects. These drugs may exhibit renoprotective properties, since they prevent the deterioration of the glomerular filtration rate and reduce the degree of albuminuria in patients with diabetes-associated kidney disease [28].

Multiple mechanisms that contribute to nephroprotective effects of SGLT2-Is in T2D patients may not only include glucose lowering-dependent but also glucose lowering-independent mechanisms (figure 3). These include: (1) Restoration of the tubule-glomerular feedback by increasing sodium delivery at macula densa, leading to afferent arteriolar constriction and reduced glomerular hyperfiltration, (2) Decreased activation of the intra-renal RAAS, which also contributes to reducing glomerular hyperfiltration, (3) Increased production of ketone bodies, which serves as an alternate fuel for adenosine triphosphate production in mitochondria, which helps in attenuating inflammation and (4) Protection against hypoxia, oxidative stress, and fibrosis [28,29].

Clinical data on SGLT2 inhibitors in diabetic nephropathy

Empagliflozin was evaluated in EMPA-REG OUTCOME trial that included patients with T2DM, established cardiovascular disease, and an eGFR of e"30 mL/min/1.73m^2. Pre-specified renal outcomes included incident or worsening nephropathy (defined as progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria (defined as urinary albumin:creatinine ratio [U_{ACR}] e"30 mg/g). Empagliflozin treatment was associated with a statistically significant 39% reduction in relative risk of incident or worsening nephropathy vs placebo. Statistically significant relative risk reductions for empagliflozin vs placebo were also observed for progression to macroalbuminuria, doubling of serum creatinine levels, and the initiation of renal-replacement therapy [30].

CREDENCE Trial assessed whether Canagliflozin compared with placebo reduces composite outcome of ESKD, doubling

of serum creatinine, or renal or CV death. Trial participants with T2DM, eGFR 30 to 90 mL/min/1.73 m^2, and UACR 300 to 5000 mg/g received standard of care including a maximum tolerated dose of an ACEi or ARB. Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred. There was a 30% reduction in primary outcome with a 32% reduction in ESKD. The study also reported a greater reduction in the estimated GFR in the canagliflozin group than in the placebo group for a between-group difference of -3.17 ml/min/1.73 m^2 [31].

CANVAS-R also evaluated renal pre-specified outcomes (composite of sustained and adjudicated doubling in serum creatinine, end-stage kidney disease, or death from renal causes; the individual components of this composite outcome; annual reductions in eGFR; and UACR). The results demonstrated renoprotective effect of Canagliflozin in people with type 2 diabetes with a reduced risk of sustained loss of kidney function, attenuated eGFR decline and a reduction in albuminuria [32].

Dapagliflozin in DKD

In DECLARE–TIMI 58 trial, 7160 T2DM patients at high risk for CV events included 7% with eGFR <60 mL/min/1.73 m^2. The pre-specified secondary outcome consisted of a composite of e"40% reduction in eGFR, new ESRD, or death from renal or CV causes. The cardio-renal secondary composite outcome was significantly reduced with dapagliflozin versus placebo (HR 0.76; excluding death from cardiovascular causes, HR for the renal-specific outcome was 0·53). A 46% reduction in sustained decline in eGFR by at least 40% to less than 60 mL/min per 1·73 m^2 was achieved with a lower risk of end-stage renal disease or renal death in the dapagliflozin group [33].

The benefits of dapagliflozin in CKD patients (with and without T2D) were consistent in those with and without cardiovascular disease in DAPA-CKD study. The hazard ratio for the composite of a e"50% sustained decline in estimated GFR or ESRD, or death from renal causes was 0.56 with dapagliflozin which was significantly lower than with placebo [34].

Findings of DERIVE study also support the positive benefit/risk profile of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (eGFR, 45-59 mL/min/1.73 m^2 ; chronic kidney disease stage 3A). The study reported greater decrease from baseline in eGFR with dapagliflozin than placebo at Week 24 [35].

Combined Role of DPP-4i and SGLT-2i in diabetic nephropathy

DPP-4i and SGLT-2i are established therapies for improving glycemic control in patients with type 2 diabetes through different mechanisms. The efficacy of DPP-4 inhibitors in lowering HbA1c does not depend on kidney function. In contrast, SGLT2 inhibitors efficacy is reduced in people with reduced kidney function, whereas the effects on bodyweight and blood pressure seem to be independent of kidney function. Therefore, combination of SGLT2 and DPP-4 inhibitors seems to be logical in patients with type 2 diabetes and chronic kidney disease in view of the complementary metabolic effects discussed [36].

The combination of SGLT-2 and DPP-4 inhibitors is also supported by DELIGHT trial which evaluated albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin in patients with T2DM and CKD. The study enrolled patients with a history of type 2 diabetes, increased urine albumin-to-creatinine ratio (UACR), an estimated GFR of 25-75 mL/min/1.73m^2 and HbA_{1c} of 7.0-11.0%, who had been receiving stable doses of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy and glucose-lowering treatment for at least 12 weeks. The difference in mean UACR change from baseline was "21·0% for dapagliflozin and "38·0% for dapagliflozin–saxagliptin. The study indicates that DPP-4i and SGLT-2i can be a potentially attractive combination to slow progression of kidney disease in patients with type 2 diabetes and moderate-to-severe chronic kidney disease [36].

Conclusion:

Ominous octet dictates that multiple drugs in combination will be required to correct the multiple pathophysiological defects involved in the development of glucose intolerance in type 2 diabetic patients. Since inadequate glycemic control often lead to kidney disease, a synergistic combination of a SGLT-2 inhibitor and a DPP-4 inhibitor provides kidney protection by targeting several complementary pathophysiological pathways. Both SGLT-2 inhibitors and DPP-4 inhibitors are already established drugs for improving glycemic control with pleotropic effects providing kidney protection, current available data holds promise for trials evaluating both in combination for patients with diabetes and diabetic nephropathy.

Acknowledgement:

Author acknowledges the contribution of Mr. Rafique Sheikh, M. Pharm (Pharmacology) for his contribution in doing literature search & helping with the preparation of manuscript.

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