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THE ROLE OF DPP-4 INHIBITORS IN TYPE-2 DIABETES PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

The most popular type of diabetes is Type-2 diabetes mellitus (T2DM) accounting for 90-95% of diagnosed diabetes and continues to overgrow worldwide and in the USA. This rapid growth may be attributed to the increased elderly population, prevalence of obesity among adults and children, socioeconomic development, urbanization, unhealthy diets, and poor physical activities. The administration of antidiabetic agents in addition to cardio-renal protection is strongly required. Adequate glycemic control must be achieved with protection against cardiovascular and renal outcomes simultaneously. DPP-4 inhibitors are novel antidiabetic agents that have recently demonstrated protection against macro and macrovascular diabetes complications, particularly cardio-renal protection. To evaluate the efficacy and safety of DPP-4 inhibitors on chronic kidney disease patients. We used the PubMed database and searched for relevant articles on the topic. We used the Mesh word searching system; DPP-4 inhibitors; complications; adverse reactions. Type-2 Diabetes mellitus; Chronic kidney disease. DPP-4 inhibitors have demonstrated promising renal protection in healthy animal studies. Nevertheless, in humans with type-2 diabetes mellitus, the renal impact is still controversial. Several randomized clinical trials support the renoprotection effect of diabetic nephropathy.

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Introduction

Bumped-up blood glucose levels are a distinguishing trait of diabetes mellitus which is a metabolic ailment that brings about a higher risk of mortality and morbidity than the general population [1]. Overall, the global incidence of diabetes has increased recently [1], and in 2015 projected statistics showed that the number of people between the age of 29-79 years with diabetes was as high as 415 million [1]. Furthermore, the prevalence of diabetes is expected to rise to 642 million by 2040 [1]. Importantly, diabetes is a significant risk factor for cardiovascular disease (CVD), which eventually the leading cause of death in the diabetic population (44% in type-1 and 52% in type-2) and diabetic kidney disease (DKD) [2, 3]. Other diabetes complications include microvascular, such as neuropathy, nephropathy, and retinopathy; in addition, macrovascular

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complications become more prevalent, comprising coronary or carotid artery disease and peripheral vascular disease with increasing diabetes duration [2].

The most popular type of diabetes is Type-2 diabetes mellitus (T2DM) accounting for 90-95% of diagnosed diabetes and continues to overgrow worldwide and in the USA [2]. This rapid growth may be attributed to the increased elderly population, prevalence of obesity among adults and children, socioeconomic development, urbanization, unhealthy diets, and poor physical activities [2, 4]. Therefore, it is essential to properly manage diabetes, focusing on the CVD risk factors since the early stages of vascular complications may already exist before diagnosis or even in the pre-diabetic status [4, 5]. The US FDA and the European Medicines Agency require all antidiabetic agents to demonstrate an acceptable and safe cardiovascular risk profile [5].

Chronic kidney disease (CKD) is a well-known T2DM complication affecting 30% to 40% of diabetic patients [6]. CKD can be identified by two distinct and complementary methods: estimated glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio (UACR) [6]. T2DM is associated with a high risk for albuminuria secondary to an inflammatory process and oxidative stress induced by chronic hyperglycemia [3]. Increased albuminuria leads to an increased risk of microvascular and macrovascular complications [3]. In addition, albuminuria has shown in different studies that it is an indicator and independent predictor for early risk and can be used to evaluate the progression and prognosis for CVD and DKD in diabetes patients [3]. The association between UACR and heart failure was reported as well in previous studies [6]. Moreover, increased urinary albuminuria levels are likely to indicate early microvascular complications and some degree of kidney damage [6].

Historically, albuminuria is diagnosed when it exceeds 30 mg/g predicting diabetic nephropathy in T2DM patients [6]. Interestingly, the association between UACR and heart failure, coronary artery disease, and incident hypertension was found in patients without diabetes [6]. Also, it was reported that drug-induced albuminuria reduction, such as renin-angiotensin-aldosterone system (RAAS) antagonists have a big influence on CVD and end-stage renal disease (ESRD) improvement [3]. Nowadays, several antidiabetic agents had demonstrated promising cardiovascular and renal protection, including sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors [3]. This literature review will focus only on DPP-4 inhibitors.

Results and Discussion

Introduction to DPP-4 Inhibitors

DPP-4 is a ubiquitous enzyme that is detectable in the endothelium of several organs, including liver, gut, kidney, lung, T-lymphocytes, and founds circulatory in the bloodstream [7, 8]. The substrates of DPP-4 are the incretins: GLP-1 and glucose-dependent insulinotropic peptide (GIP), which have been well validated in humans [7]. DPP-4 works by cleaving and blocking GLP-1 within a few minutes [7], released by the small intestinal endocrine cells after food ingestion [9]. As a result, GLP-1 levels, which are low in diabetic patients, become elevated and stimulate glucose-dependent insulin release from the pancreas, provide satiety by acting on the hypothalamus, and simultaneously inhibit hepatic glucagon secretion [8, 9].

Further, many T2DM patients were found to have weak responses to GIP [9]. DPP-4 also cleaves several other peptides apart from GLP-1 and GIP, which might offer beneficial effects for glycemic control and beta-cell functionality when inhibited by DPP-4 inhibitors [9]. Hence, DPP-4 inhibitors lowered blood glucose concentration, HbA1c in T2DM patients [8] and resulted in maintained beta-cell mass and islet function [9]. Additional mechanisms of DPP-4 inhibitors include reduction in gastrointestinal motility and slowing of gastric emptying [8]. Because incretins secretion is glucose-dependent, DPP-4 inhibitors are not expected to induce hypoglycemia in the fasting status [9, 10].

In trials comparing DPP-4 inhibitors to placebo, it was associated with a slight weight increase of 0.5kg [9]. Sitagliptin was found in non-inferiority trials to have a favorable weight profile when compared to glipizide [9]. Moreover, sitagliptin and vildagliptin use were associated with improved levels of triglycerides, low and high-density lipoproteins [9]. Additionally, DPP-4 inhibitors with narrow or wide specificity may encounter a place beyond diabetes to treating skin fibrosis and immune diseases, in leukapheresis and stem cell transplantation, and in preventing ischemic or reperfusion damage [9].

The Potential Renal Protection Site of DPP-4 Inhibitors in Type-2 Diabetes Mellitus

Notably, the DPP-4 enzyme is observed in various renal membrane-bound locations, such as vascular smooth muscle cells in the afferent arteriolar, mesangial cells, podocytes, and proximal tubular cells [11, 12]. DPP-4 (aka as CD26) is expressed as a type II transmembrane glycoprotein, with a short 6-amino acid cytoplasmic tail. Its monomer weight molecular weight is 110 kDa however it usually shows its activity as a dimer [12]. Besides, DPP-4 inhibitors appear to have beneficial albuminuria effects, similar to those with GLP-1 agents [11].

Experimental studies have revealed that Brain Natriuretic Peptide (BNP) is cleaved by DPP-4, resulting in minor natriuretic, diuretic, and vasodilatory activity [12]. Nevertheless, It was not found that the elevated BNP due to the DPP-4 inhibitor's effect is associated with the pathogenesis of DKD [12]. Also, the erythropoietin hormone is cleaved by DPP-4; however, the clinical importance of DPP-4 inhibitors for erythropoietin remains unknown [12]. The development of DKD is primarily induced by inflammation, oxidative stress, and fibrosis [12]. Inflammatory signaling pathways and oxidative stress encourage the excretion of renal transforming growth factor (TGF)-beta and the fabrication of extracellular matrix (ECM) via NF-kB activation, which leads to glomerulosclerosis and tubulointerstitial fibrosis [12]. In particular, saxagliptin limits interstitial

fibrosis, glomerular hypertrophy, and macrophage infiltration mediated by NF-kBp65 [13]. Epithelial-to-mesenchymal transition (EMT) is encountered as a basis of ECM production from fibroblasts in DKD [12].
Tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6, and IL-18 all being inflammatory cytokines lead to an expression of chemokines, incorporating monocyte chemoattractant protein (MCP)-1 [12]. The latest found to influence macrophage infiltration toward mesangial cells [12]. Importantly, given that the daily dose is regulated adequately following the eGFR reductions, DPP-4 inhibitors can be safely used in CKD patients at any stage with an exception to the dosage of linagliptin that regardless of the eGFR it can be on the same amount. This is due to its predominantly hepatic elimination [14]. Moreover, animal experimental studies have suggested that the DPP-4 inhibitors' nephroprotective properties may lead to a reduction of stress caused by oxidation and swelling and improvement of endothelial dysfunction [14]. In a large retrospective cohort study, DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin, vildagliptin, gemigliptin) effectively decreased albumin secretion after just a year and after a 4-year period, they were able to limit the decline of eGFR in Japanese diabetic patients [14].
Nonetheless, in a recent analysis of the metadata of 36 randomized controlled trials (RCTs) that were double-blind, with DPP-4 inhibitors for a total of 54,664 patients, the result was no outstanding differences in renal failure comparing DPP-4 inhibitors with placebo or other active antidiabetic agents [14]. Based on an initial study that evaluated the potential effects of vildagliptin on LDL heterogeneity and albuminuria among patients with T2DM complicated by nephropathy, the UACR was reduced by 44.6%, despite eGFR remaining unchanged [13]. Another pilot study evaluated linagliptin's anti-inflammatory effects in T2DM patients and evaluated any various markers of stress by oxidation, C-reactive protein (CRP), UACR, eGFR, and urinary liver fatty acid-binding protein (L-FABP) as a tubulointerstitial injury marker [13]. A quarter year later, L-FABP and oxidative stress indicators significantly decreased, regardless of HbA1c, while CRP, UACR, and eGFR remained constant [13].
On the other hand, a meta-analysis of 19 studies investigating the renal effect of DPP-4 inhibitors in T2DM patients [15]. It revealed that DPP-4 inhibitors had a renoprotective effect by reducing the risk of ESRD in T2DM patients compared to placebo or other antidiabetic medications [15]. The renoprotective mechanism of DPP-4 inhibitors was suggested to be related to reducing micro and macroalbuminuria [15]. Further, preclinical studies found that DPP-4 inhibitors provide renoprotection in DKD by GLP-1 dependent and independent effects: lessening the stress of oxidation, swelling, and histopathologic modifications in kidney injury [15, 16].
Moreover, the DPP-4 substrate, the incretins, mediate vasodilatation of glomerular capillaries, which increase renal blood flow and maintain GFR in healthy rodents [17]. Also, it has been recently found that GLP-1 receptor activation in the atrium can indirectly induce natriuretic and vasorelaxant impact by releasing Atrial Natriuretic Peptide (ANP) [17]. The latter, in turn, stimulates its receptors in the kidney [17]. In addition, DPP-4 inhibitors induced natriuresis on T2DM patients, mainly on the distal renal tubule, opposite to SGLT-2 inhibitors, which act on the proximal tubules [15].
Therefore, through antioxidation, anti-inflammation, and anti-fabrication effects albuminuria is limited by DPP-4 inhibitors [15]. DPP-4 inhibitor's antioxidant effect; mitochondrial dysfunction and apoptosis; connective tissues growth factor suppression; restraint of TGF-beta related fibrosis and nuclear factor (NF)-kB [18]. P65-mediated macrophages infiltration; lessening of renal tubulointerstitial fibronectin; up adjustment of stromal cell-derived factor-1; repression of advanced glycation end-products; control of proliferation of preglomerular vascular smooth muscle and mesangial cells; and dwindling numbers of high blood pressures were also reported [18].
Despite these promising results, however, the renal effect on human clinical trials is still controversial in affected persons with T2DM and has mainly shown safety rather than an actual impact on renal outcomes [18]. In the SAVOR-TIMI 53 study, saxagliptin significantly reduces UACR compared to placebo, primarily driven by the microalbuminuria reduction effect, despite no association between improved UACR and HbA1c [18, 19]. Besides, the incidence of UACR headway was considerably decreased with saxagliptin in comparison to placebo in all DKD patients apart from those with extreme kidney damage [10, 19, 20].

Conclusion

DPP-4 inhibitors are novel antidiabetic agents that were introduced and approved by FDA in 2006. Since then, DPP-4 inhibitors have had a promising impact on micro and macrovascular complications of type-2 diabetes mellitus. Further, DPP-4 inhibitors provide cardiovascular and renal protection regardless of their antidiabetic effect as demonstrated. Although the mechanism of cardio-renal protection has been well-known and established, clinical trials have failed to make a consensus. Since it is still a debatable topic, further clinical trials assessing the effect of cardio-renal protection of DPP-4 inhibitors would be recommended.

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