Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 361–373

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

REVIEW

Dipeptidyl peptidase-4 inhibition in chronic kidney disease and potential for protection against diabetes-related renal injury

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Received 6 August 2015; received in revised form 21 December 2015; accepted 7 January 2016
Available online 13 January 2016

KEYWORDS
Type 2 diabetes mellitus;
Dipeptidyl peptidase-4 inhibitor;
Chronic kidney disease;
Diabetic nephropathy;
Estimated glomerular filtration rate;
Albuminuria

Abstract *Aims:* Type 2 diabetes mellitus (T2DM) is associated with a high risk of chronic kidney disease (CKD). About 20% of patients with T2DM have CKD of stage ≥ 3; up to 40% have some degree of CKD. Beyond targeting all renal risk factors together, renin–angiotensin–aldosterone system blockers are to date the only effective mainstay for the treatment of diabetic kidney disease (DKD). Indeed, several potentially nephroprotective agents have been in use, which have been unsuccessful. Some glucose-lowering agents, including dipeptidyl peptidase-4 inhibitors (DPP-4i), have shown promising results.

Here, we discuss the evidence that glucose lowering with DPP-4i may be an option for protecting against diabetes-related renal injury.

Data synthesis: A comprehensive search was performed of the literature using the terms "alogliptin," "linagliptin," "saxagliptin," "sitagliptin," and "vildagliptin" for original articles and reviews addressing this topic.

DPP-4i are an effective, well-tolerated treatment option for T2DM with any degree of renal impairment. Preclinical observations and clinical studies suggest that DPP-4i might also be a promising strategy for the treatment of DKD. The available data are in favor of saxagliptin and linagliptin, but the consistency of results points to the possible nephroprotective effect of DPP-4i. This property appears to be independent of glucose lowering and can potentially complement other therapies that preserve renal function. Larger prospective clinical trials are ongoing, which might strengthen these hypothesis-generating findings.

Conclusions: The improvement in albuminuria associated with DPP-4i suggests that these agents may provide renal benefits beyond their glucose-lowering effects, thus offering direct protection from DKD. These promising results must be interpreted with caution and need to be confirmed in forthcoming studies.

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http://dx.doi.org/10.1016/j.numecd.2016.01.001

Introduction

The prevalence of chronic kidney disease (CKD) is >10%, exceeding 20% in subjects older than 60 years and 30–40% in high-risk subpopulations, such as individuals with diabetes [1,2]. Independent of confounders, both in the general population and in high-risk categories, strong, graded, and consistent associations are noted between renal and cardiovascular outcomes and the two hallmarks of CKD, reduced glomerular filtration rate (GFR) and increased urinary albumin excretion (UAE) [3,4]. In the German Chronic Kidney Disease (GCKD) cohort, 35% of subjects with moderate CKD (estimated GFR 30–60 ml/min/1.73 m^2 or overt proteinuria at higher eGFR) had diabetes, whereas 43% were obese [5]. Despite the great advances in glycemic and blood pressure (BP) control, diabetic kidney disease is becoming highly prevalent as a cause of end-stage renal disease (ESRD) in all developed countries. Due to their hemodynamic, antihypertensive, anti-inflammatory, and anti-fibrotic effects, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARB) are actually the mainstays of the pharmacological treatment for diabetic kidney disease [6]. However, even with the current use of ACE inhibitors, ARBs, and, more recently, direct renin inhibitors [7], the burden of diabetic kidney disease remains very high, if not increasing. Furthermore, over the past years, a number of high-profile clinical trials have reported failed treatments [8,9]. Consistently, apart from renin–angiotensin–aldosterone system (RAAS) blockers, several novel potentially nephroprotective agents such as paracalcitol in early diabetic kidney disease [10], endothelin receptor antagonists in overt diabetic nephropathy [11], and bardoxolone methyl in advanced-stage kidney disease [12] have failed to meet the expectations [13]. Thus, although research into novel therapies to treat diabetic kidney disease is expanding, to date no new formulations have been applied to clinical practice.

Incretin-based therapy with glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors is a relatively new therapeutic option for type 2 diabetes mellitus (T2DM) with proven efficacy, tolerability, and safety. In particular, DPP-4 inhibitors are oral, weight neutral, blood glucose-lowering drugs with no hypoglycemic effect. Their activity is based on the inhibition of the DPP-4 enzyme, which mediates the degradation of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). This class of drugs includes sitagliptin, vildagliptin, saxagliptin, and, more recently, linagliptin and alogliptin. Several review articles have addressed the pharmacokinetics and clinical use of DPP-4 inhibitors (and GLP-1 receptor agonists) in patients with T2DM and renal impairment. They concluded that DPP-4 inhibitors represent an effective and well-tolerated option for the treatment of patients with T2DM and any degree of CKD, provided the therapeutic products are used according to their labeling [14–16]. Furthermore, cumulative evidence, not only from preclinical studies but also from clinical trials, has shown that DPP-4 inhibition may also exert beneficial effects on kidney function, thus exerting some protective effect against the development or worsening of diabetic nephropathy. Herein, we provide an overview of the clinical observations indicating a direct nephroprotective effect of incretin-based therapy with DPP-4 inhibitors in the setting of diabetic kidney disease. For this purpose, a short preliminary section describes other different "conventional" antihyperglycemic agents with nephroprotective properties independent of their blood glucose-lowering effects, apart from DPP-4 inhibitors (or GLP-1 receptor agonists). However, both reviewing preclinical data that indicate the nephroprotective properties of DPP-4 inhibitors and discussing potential mechanisms for these effects are beyond the scope of this study.

Conventional antihyperglycemic drugs and potential for nephroprotection

In ADOPT (A Diabetes Outcomes Prevention Trial), initial monotherapy with the thiazolidinedione rosiglitazone led to more persistent glycemic control than metformin or glyburide in 4351 patients with recently diagnosed drug-naïve T2DM. Over the 5-year follow-up, the long-term effects of these three glucose-lowering medications on UAE as measured by the albumin/creatinine ratio (ACR) and the modification of diet in renal disease (MDRD)-estimated GFR were examined. Over a period of 6 months to 5 years, the ACR increased by 1.77% annually with rosiglitazone, compared to the annual 5.2% increase with metformin ($p = 0.052$) and 4.6% per year with glyburide. However, there was no difference among the groups in the incidence of emergent albuminuria (ACR $\geq$ 30 mg/g: 18.2% rosiglitazone, 22.5% metformin, and 20.9% glyburide), or impaired eGFR (<60 ml/min/1.73 m^2) [17]. Consistently, a meta-analysis of short-term studies on the effect of rosiglitazone or pioglitazone on 2860 patients with normoalbuminuria or microalbuminuria showed a greater reduction of UAE or urinary protein excretion in subjects treated with thiazolidinediones compared with active comparators or placebo [18]. A systematic review on the comparative efficacy and safety of oral hypoglycemic agents for T2DM prompted by the Agency of Healthcare Research and Quality (AHRQ) and published in 2011 concluded that the strength of evidence was low or insufficient to support the comparative effects of diabetic medications on long-term clinical outcomes of mortality and macrovascular and microvascular complications of diabetes, including nephropathy. In particular, pioglitazone was found to reduce the urinary ACR in two trials (by 15% and 19%) compared with metformin, suggesting a nephroprotective effect. The strength of this evidence was deemed as moderate [19].

More recently, the comparative efficacy of oral antidiabetic drugs (OADs) on kidney function was evaluated using a retrospective cohort of 93,577 diabetic patients from the Veterans Administration Database. These patients filled an incident OAD monotherapy prescription for metformin, sulfonylurea, or rosiglitazone and had an eGFR of $\geq$60 ml/min/1.73 m^2. Compared with patients using