РОЛЬ ПРЕПАРАТОВ ИНКРЕТИНОВОГО РЯДА В ЛЕЧЕНИИ ДИАБЕТИЧЕСКОЙ НЕФРОПАТИИ

© Paola Fioretto*, Andrea Frascati

Department of Medicine, University of Padova, Падуя, Италия

Диабетическая нефропатия (ДН) – серьезное микрососудистое осложнение сахарного диабета (СД), также являющееся основной причиной терминальной стадии почечной недостаточности и ассоциированное с повышенным риском сердечно-сосудистых заболеваний и смертности. Несмотря на достижения в поддержании оптимальных показателей гликемии и артериального давления, приблизительно у 20–40% пациентов с СД развивается ДН. Тщательный контроль гликемии и АД замедляет снижение расчетной скорости клубочковой фильтрации и альбуминурии, что позволяет отсрочить дебют и развитие диабетической нефропатии. Препараты инкретинового ряда, такие как агонисты рецептора глюкагоноподобного пептида-1 (ГПП-1) и ингибиторы дипептидилпептидазы-4 (ДПП-4), широко используются в качестве сахароснижающей терапии и демонстрируют улучшение почечных исходов при ДН. В данном обзоре обсуждаются негликемические свойства препаратов инкретинового ряда и их нефропротективное действие на компоненты метаболического синдрома: ожирение, артериальную гипертензию и дислипидемию; уменьшение оксидативного стресса и воспаление; увеличение натрийуреза.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 2 типа; диабетическая болезнь почек; диабетическая нефропатия; инкретины; ингибиторы ДПП-4; агонисты рецептора ГПП-1

ROLE OF INCRETIN BASED THERAPIES IN THE TREATMENT OF DIABETIC KIDNEY DISEASE

© Paola Fioretto*, Andrea Frascati

Department of Medicine, University of Padova, Italy

Diabetic kidney disease (DKD), a serious microvascular complication of diabetes mellitus is a leading cause of end-stage renal disease and is associated with an increased risk of cardiovascular morbidity and mortality. Despite advancements in blood glucose and blood pressure (BP) control, ~20% to 40% of patients with diabetes mellitus develop DKD. Intensive glycaemic and BP control positively influence decline in estimated glomerular filtration rate and albuminuria, thereby delaying the onset and progression of diabetic nephropathy. Incretin based therapies namely glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used glucose lowering agents and have shown favorable renal outcomes in DKD. This article discusses the extra-glycaemic properties of incretin based therapies and their renoprotective effects on components of the metabolic syndrome, including obesity, hypertension and dyslipidaemia; reduction in oxidative stress and inflammation; and increase in natriuresis.

KEYWORDS: type 2 diabetes mellitus; diabetic kidney disease; diabetic nephropathy; incretins; DPP-4 inhibitors; GLP-1 receptor agonists

Diabetic kidney disease (DKD) is a serious microvascular complication of diabetes mellitus and is a leading cause of end-stage renal disease (ESRD). It is characterised by a progressive decline in kidney function, resulting in increased albuminuria (>300 mg/24h or >200 μg/min), decreased glomerular filtration rate (GFR), elevated blood pressure (BP) and increased morbidity and mortality due to cardiovascular complications [1].

NATURAL HISTORY OF DIABETIC NEPHROPATHY

The pathophysiology of DKD is complex and multifactorial, involving both genetic and environmental factors [2]. At the time of diagnosis, there is an increase in GFR by 25%–50% in ~70% of patients with type 1 diabetes mellitus (T1DM) and ~50% of patients with type 2 diabetes mellitus (T2DM) which is accompanied by tubular hyperplasia, hypertrophy, and increased kidney size. Although the above features of glomerular hyperfiltration are all clearly manifested in T1DM, in patients with T2DM, the symptoms depend on the mean age, duration of diabetes, alongside variability in GFR, which is influenced by glycaemic and BP control [2, 3].

Despite the increased awareness of the risk factors and therapeutic advancement in BP, glycaemic and lipid control, ~20% to 40% of patients with diabetes mellitus develop DKD [1, 2]. About 3% of newly diagnosed patients with T2DM are reported to have overt nephropathy [3]. In T2DM, DKD is usually preceded by long-standing cardiovascular risk factors such as obesity, hypertension and dyslipidaemia besides chronic hyperglycaemia [2, 4]. Over the decades, there has been a significant reduction in the incidence of diabetes-related complications such as stroke, acute myocardial infarction, amputations and death due to hyperglycaemic crisis, however, there has only been a small decrease in the incidence of ESRD [5]. Thus, given the severity of DKD there is a need for effective management strategies focusing on a multidimensional approach to prevent and delay the progression of the disease. In addition to the currently used markers such

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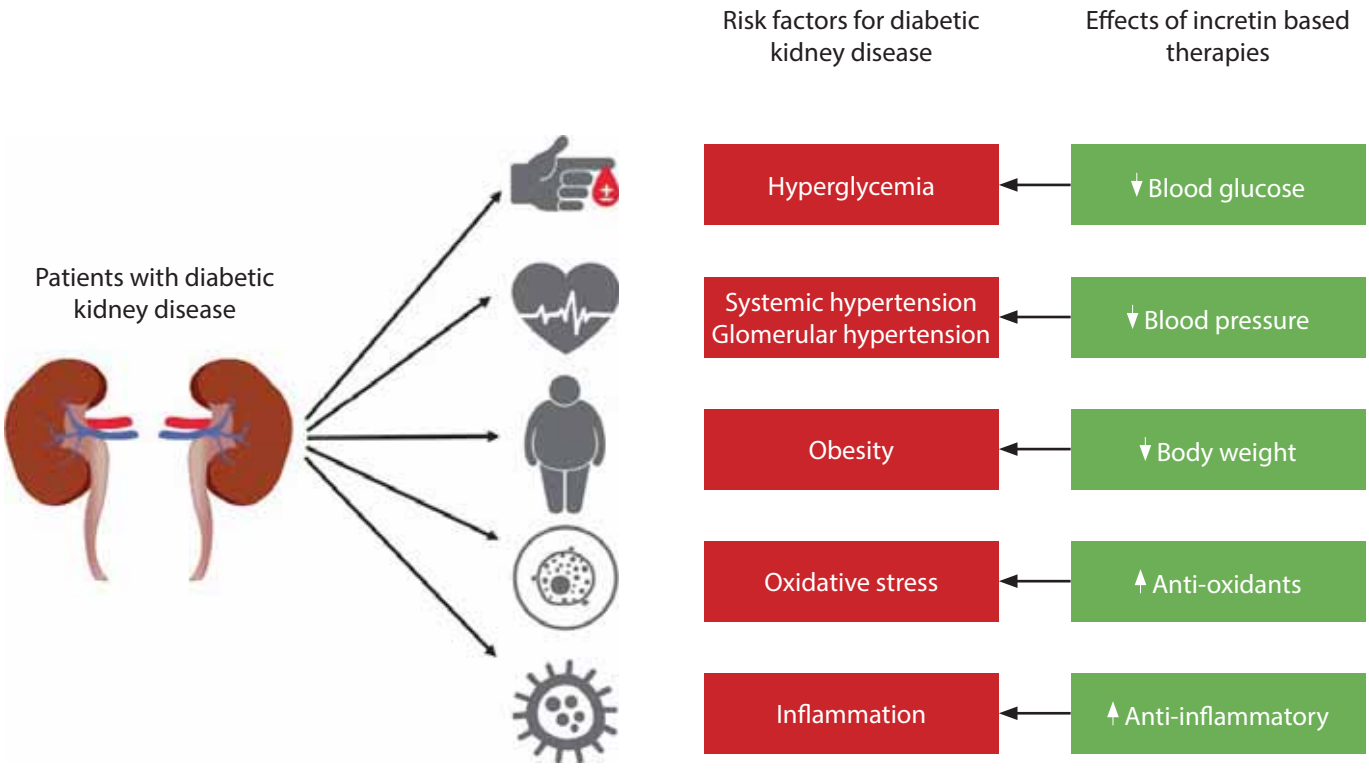

Fig. 1. Renoprotective effects of incretin based therapies

as estimated GFR (eGFR), and albumin-creatinine ratio, there is a need for other well-defined urine and plasma biomarkers to identify populations at risk of progressive DKD and to improve clinical outcomes by individualising treatment strategies [6].

TREATMENT OF DIABETIC NEPHROPATHY

Intensive glycaemic and BP control positively influence decline in eGFR and albuminuria, thereby delaying the onset and progression of diabetic nephropathy [7]. Long-term studies such as UKPDS and ADVANCE in patients with T2DM have shown that intensive glycaemic control result in sustained reductions in renal complications that can last several years [8, 9].

Results from the UKPDS demonstrated that intensive glycaemic and BP control in patients with T2DM resulted in the reduction of relative risk for development of microalbuminuria by 33% and microvascular outcomes by 25% at 12 years [8, 10]. The benefits of intensive glycaemic control for 5 years was demonstrated from the findings of the ADVANCE trial, with a 65% reduction in the risk of ESRD [9]. Further, the risk for impaired GFR was reduced by 50% in the intensive treatment group in patients with T1DM from a long-term follow-up (22 years) DCCT-EDIC trial [11].

Effect of incretin-based therapies on renal risk factors

Chronic hyperglycaemia, hypertension and dyslipidaemia lead to haemodynamic changes that modulate intracellular signaling pathways, transcription factors, cytokines, chemokines, and growth factors responsible for the development and progression of DKD [12]. Incretin-based therapies glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors have shown favourable renal outcomes in DKD. In addition to glycaemic control, both GLP-1 RAs and DPP-4 inhibitors extend their renoprotective effects on components of the metabolic syndrome, including obesity, hypertension and dyslipidaemia; reduction in oxidative stress and inflammation; and increase in natriuresis (Figure 1) [2].

Renoprotective effects of GLP-1 receptor agonists

In healthy subjects, GLP-1 infusion markedly increased urinary sodium excretion, although no significant changes were observed in pro atrial natriuretic peptide (proANP) or pro B-type natriuretic peptide (proBNP) concentrations [13]. Similarly, in a randomised, double-blind, placebo-controlled trial in patients with T2DM who were overweight and had normal renal function (GFR ≥60 mL/min/1.73 m2), treatment with exenatide increased proximal sodium excretion, but did not affect GFR, renal plasma flow, and glomerular pressure [14].

A short-term study demonstrated that liraglutide decreased the proximal tubular sodium reabsorption without altering renal haemodynamics [15]. Furthermore, 12-week treatment with liraglutide in patients with T2DM and persistent albuminuria (urinary albumin-creatinine ratio >30 mg/g) and eGFR ≥30 mL/min/1.73 m2 showed clinically relevant reduction of 32% (p=0.017) in urinary albumin excretion rate. In addition, liraglutide demonstrated reductions in plasma renin activity (35%, p=0.060), mean plasma concentrations of renin (37%, p=0.030), and angiotensin II (43%, p=0.022), demonstrating its role in renin-angiotensin-system (RAS) inhibition [16].

After treatment with exenatide in patients with T2DM and microalbuminuria, significant reductions in urinary excretion of albumin, transforming growth factor-β1 and type IV collagen, and lowering of body mass index and systolic BP were observed, demonstrating the renoprotective effects of exenatide beyond glycaemic

control [17]. The 52-week DURATION-2 trial revealed that T2DM patients treated with exenatide throughout the study showed reductions in glycated haemoglobin (HbA1c), body weight and BP, along with significant decreases in the cardiovascular markers such as the albumin-creatinine ratio (34%, p<0.05), compared to patients who were switched to sitagliptin (18%, p<0.05) and pioglitazone (23%, p<0.05) [18].

In T2DM patients with a high risk for cardiovascular disease, the incidence of a renal microvascular events (including macroalbuminuria, doubling of serum creatinine, ESRD, and renal death) was lower in the liraglutide group than in the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.67–0.92; p=0.003) as demonstrated in the LEADER trial [19]. Fewer patients in the liraglutide group showed new onset of persistent albuminuria (hazard ratio [HR]: 0.74; 95% CI, 0.60–0.91; p=0.004) [20]. Similar results for the renal outcomes in T2DM patients with eGFR ≥30 mL/min/1.73 m2 were observed in the EMPA-REG OUTCOME trial with a sodium-glucose co-transporter-2 (SGLT-2) inhibitor. Patients treated with empagliflozin showed slower progression of kidney disease (HR: 0.61; 95% CI, 0.53–0.70; p<0.001) and lower incidence of renal events compared to placebo [21].

Other renoprotective functions of GLP-1 RAs, such as reduction of oxidative stress and anti-inflammatory effects, have been demonstrated in animal studies [22, 23]. Treatment with liraglutide suppressed the progression of nephropathy in KK/Ta-Akita mice by reducing albuminuria and mesangial expansion, decreasing levels of glomerular superoxid e and renal nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and elevating renal cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activity. These effects were lost in the presence of inhibitors for adenylate cyclase and PKA. This suggests that GLP-1 plays a key role in the protection against increased renal oxidative stress under chronic hyperglycaemia by inhibiting NADPH oxidase and activation of the cAMP-PKA pathway [22]. Studies with a streptozotocin-induced rat model of T1DM have shown that exendin-4 exerts anti-inflammatory actions by directly acting on GLP-1 receptors and by suppressing the production of pro-inflammatory cytokines and intercellular adhesion molecule-1 [23].

Renoprotective effects of DPP-4 inhibitors

Inhibition of DPP-4 has shown to promote natriuresis by blocking sodium reabsorption at the distal convoluted tubule after short-term treatment (1 month) with sitagliptin in patients with T2DM, while not altering the renal haemodynamic mechanisms [24]. Conversely, GLP-1 RAs and SGLT-2 inhibitors act at the proximal tubule.

Studies have shown that the DPP-4 enzyme has multiple substrates besides GLP-1 and gastric inhibitory polypeptide (GIP). Stromal cell–derived factor (SDF)-1α, a chemokine widely expressed in distal tubular cells, is a physiological substrate to DPP-4. Treatment with sitagliptin has shown to increase plasma levels of intact SDF-1α, which has demonstrated natriuretic effects in preclinical studies [24].

Treatment with linagliptin in addition to renin–angiotensin–aldosterone system (RAAS) inhibitors resulted in a significant reduction in albuminuria (32%; 95% CI, −42−−21; p<0.05) in T2DM patients with renal dysfunction (urinary albumin-creatinine ratio of 30–3000 mg/g) after 24 weeks. These results suggest an additive effect on lowering microalbuminuria with a combination of RAAS and DPP-4 inhibitors [25]. Saxagliptin also decreased the albumin-creatinine ratio in a large and heterogeneous population of T2DM patients with normo-, micro-, and macroalbuminuria, irrespective of eGFR at baseline, in the SAVOR-TIMI trial [26].

Other substrates of the DPP-4 enzyme, such as ANP, substance P, meprin A subunit β, and neuropeptide Y, are known to have anti-inflammatory, natriuretic, and vasoactive effects, indicating that the effects of DPP-4 inhibition are independent of GLP-1 [2].

CONCLUSION

Treatment of DKD is challenging because of the progressive nature and multiple pathophysiological pathways involved. A multifactorial approach of glucose, BP and lipid control along with RAS blockade have been shown to be effective in improving renal and cardiovascular outcomes. Nevertheless, further research on the pathophysiological mechanisms related with the progression of DKD are needed to identify novel treatment targets. Incretin-based therapies such as GLP-1 RAs and DPP-4 inhibitors confer renoprotection and decelerate the progression of DKD by inhibiting inflammation and oxidative stress as seen in animal studies. GLP-1 RAs in addition to HbA1c reduction, lower BP and weight, increase natriuresis and slow the progression to macroalbuminuria. Also, DPP-4 inhibitors have a positive influence on albuminuria. These agents represent a useful treatment paradigm in patients with T2DM and kidney disease. However, most of the results generated on renal function and clinical renal outcomes are safety data rather than true efficacy endpoints, emphasising the need for further studies with renal endpoints.

ADDITIONAL INFORMATION

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ИНФОРМАЦИЯ ОБ АВТОРАХ [AUTHORS INFO]

*__Paola Fioretto__, MD, PhD, Department of Medicine; address: Via Giustiniani 2, 35128 Padova, Italy; ORCID: http://orcid.org/0000-0003-3445-0387; e-mail: paola.fioretto@unipd.it

__Andrea Frascati__, MD, Department of Medicine; e-mail: andrea.frascati@unipd.it

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