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Medicine

EFFECTS OF LINAGLIPTIN VERSUS GLIMEPIRIDE AS METFORMIN ADD-ON ON RENAL PHYSIOLOGY IN OVERWEIGHT TYPE 2 DIABETES PATIENTS

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Introduction

Over the past two decades, several new glucose lowering medications have been introduced for the treatment of type 2 diabetes (T2D). Even though the growing number of therapeutic options, however, glycemic management of T2D patients remains far from optimal. Even though most major guidelines in the USA, Europe and Asia recommend setting a HbA1c target of <7%, a substantial proportion of patients with T2D do not achieve this level of glycemic control.[1]

Tight glycemic control can bring long-term microvascular and possible macrovascular advantages, but it also may increase hypoglycaemia, especially when classical glucose-lowering medications with high risk for hypoglycaemia (insulin, sulfonylureas) are used for intensive therapy. But it is possible that the risk–benefit ratio of this strategy could be more favourable with the use of modern oral antidiabetic drugs (OADs), such as dipeptidyl peptidase- 4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors, which improve glycemic control without substantially increasing the risk of hypoglycaemia. [1]

Dipeptidyl peptidase 4 (DPP4) inhibitors, also known as gliptins, are a rapidly expanding class of oral antidiabetic drugs for the management of type 2 diabetes mellitus (T2DM). In 2011, the DPP4 inhibitor linagliptin was approved by the FDA and the European Medicines Agency (EMA) for use in patients with T2DM as a second-line therapy to add on to metformin either alone or in combination with another second-line treatment. Gallwitz et al demonstrated that linagliptin has efficacy and safety comparable to that of the sulphonylurea glimepiride as a second-line add-on therapy to metformin in patients with T2DM and also that treatment with linagliptin results in fewer adverse outcomes than does treatment with glimepiride. [2]

Preclinical studies, placebo-controlled trials, and cardiovascular outcome trials (CVOTs) recommend that DPP-4i may prevent albuminuria onset/progression beyond glucose lowering. Underlying mechanisms may include direct actions on the kidney, as membrane-bound DPP-4 and glucagon-like peptide 1 (GLP- 1) receptors (GLP-1R) are putatively expressed in various nephron segments. It was reported that sitagliptin modestly reduced estimated glomerular hydraulic pressure (PGLO) and increased fractional excretion (FE) of sodium (FENa) in T2DM patients versus placebo. Even though GLP-1R–mediated effects may underlie actions of DPP-4i on renal vasculature/ tubules, GLP-1–independent effects of this drug class may also be implicated. Glucose-lowering per se influences renal physiology, underscoring the importance of attainment of glycemic equipoise. [3]

Further, linagliptin can lower albuminuria on top of the recommended standard treatment in patients with type 2 DM. Tsuprykov et al reported that linagliptin delays renal disease progression in a nondiabetic, nonglucose- dependent rodent chronic kidney disease (CKD) model. DPP-4 inhibition with linagliptin may therefore be a novel approach for the treatment of CKD in general. [4]

Effect of Linagliptin on Renal Progression in Type-2 Diabetes Mellitus Patients with Chronic Kidney Disease

A prospective randomized controlled study involving stage 3–4 CKD patients who had estimated glomerular filtration rate (eGFR) lower than 60 mL/min were randomized into 2 groups. In the first group, linagliptin 5 mg was added in addition to the background insulin therapy whereas in the second group, patients continued their insulin therapy. Patients were followed up at 3-month intervals for one year. [4]
In total, the study included 164 patients (90 patients in linagliptin group, 74 patients in other group) with a mean age of 67.5 ± 8.8 years. eGFR significantly increased in linagliptin group ($p = 0.033$) but decreased in another group ($p = 0.003$). No significant change was observed in total insulin dose in linagliptin group ($p = 0.111$), but then in other group, total insulin dose significantly increased ($p < 0.001$). Proteinuria levels reduced in both groups, but there was no significant change. In the multiple logistic regression analysis, male gender and proteinuria occurred as variables that showed significant association with increased risk and the use of linagliptin emerged as variable that showed significant association with decreased risk for CKD progression.[4]

Table 1: Comparison of renal and diabetic parameters between basal and twelfth month measurements.

Variable	Group 1[a] n=90			Group 2[a] n=74		
	Basal	Twelfth month	p	Basal	Twelfth month	p
eGFR, mL/min	39.4 ± 10.4	41.9 ± 14.3	0.033	37 ± 11.9	33.6 ± 14.7	0.003
HbA1C, %	8.4 ± 1.6	8.2 ± 1.4	0.194	7.7 ± 1.1	7.8 ± 1.2	0.188
Uric acid, mg/dL	7.6 ± 1.9	6.9 ± 1.8	0.014	7.4 ± 1.9	7.8 ± 1.8	0.179
UPCR, mg/g	1165.8 ± 2251.6	814.8 ± 1301.1	0.107	1370.9 ± 1838.7	1046.3 ± 1449.3	0.161
Total insulin dose, U	44.5 ± 29.7	47.2 ± 33.4	0.111	62.5 ± 40.1	70.9 ± 44.9	<0.001

a Group 1 patients received linagliptin plus insulin, group 2 patients received only insulin. eGFR: estimated glomerular filtration rate, UPCR: urinary protein excretion, BUN: blood urea nitrogen.

Hence, linagliptin in T2D patients with CKD can improve renal progression without significant effect on proteinuria and glucose control. Further, linagliptin can be a new therapeutic option for treating diabetic nephropathy. [4]

Effects of Linagliptin on Renal Endothelial Function in Patients with Type 2 Diabetes In a randomised, double-blind, parallel-group, investigator-initiated trial, 62 patients with type 2 diabetes were randomly assigned to receive linagliptin 5 mg (n =30) or placebo (n=32) for 4 weeks. [5]

The change in RPF due to NG-monomethyl-L-arginine (L-NMMA) was smaller after 4 weeks of treatment with linagliptin compared with

placebo or percentage values [p=0.046, Fig. 1]), indicating lower basal NO activity after treatment with linagliptin. [5]

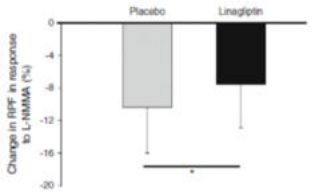

Figure 1 : Change in RPF in response to L-NMMA after 4 weeks of treatment with placebo or linagliptin. Data are shown as mean ± SD; *p<0.05

After 4 weeks of treatment, there was no difference in the response of Urinary albumin to creatinine ratio (UACR) due to L-NMMA between linagliptin and placebo (median [interquartile range]: 59.5 [11.7–160]%) vs 20.4 [−8.5 to 139]%, p=0.233). At baseline (p =0.043) and after 4 weeks of treatment with placebo (p = 0.001) there was a significant increase in UACR in response to L-NMMA. This increase in response was enhanced after 4 weeks of placebo versus baseline (p = 0.059), pointing toward an upregulation of NO activity in the ('untreated') placebo group, whereas UACR in response to L-NMMA did not change in the linagliptin group (p=0.276) (Fig. 2). [5]

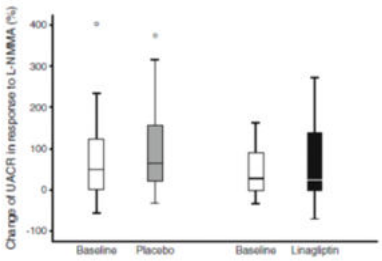

Figure 2 : Change in UACR in response to L-NMMA at baseline and after placebo or linagliptin treatment. Data are shown as median, interquartile range and outliers (open circles) Hence, the study suggests that treatment with the dipeptidyl peptidase-4 inhibitor linagliptin for 4 weeks prevented the impairment of renal endothelial function due to hyperglycaemia in type 2 diabetes. [5]

Metformin: A Candidate Drug for Renal Diseases

In many clinical studies, metformin has demonstrated to improve survival of acute kidney injury (AKI) and CKD patients. In a large cohort of over 25,000 patients with T2D, Bell et al. [6] provided a reassuring message of the safety of metformin in patients with or without CKD, as mortality was not adversely affected by metformin usage. Metformin did not increase the incidence of AKI, and survival rates were higher in patients with AKI previously treated with metformin. In a retrospective cohort study, Stephen et al. [7] connected Scientific Registry of Transplant Recipients data for all incident kidney transplants from 2001 until 2012, and national pharmacy claims. They found that survival was superior for all outcomes for recipients who filled metformin claims versus those who filled non-metformin agent claims. In an open cohort study of 469,688 T2D patients, the relationship between a range of complications and antidiabetic therapy was analysed. Severe kidney failure, including dialysis treatment, kidney transplant, and CKD stage 5, were among the five pre-specified key outcomes. Metformin was associated with a significantly decreased risk of severe kidney failure compared with non-use, whereas sulfonylureas and insulin increased this risk.[8] In a systematic review involving 17 observational studies, metformin use appeared to be associated with decreased all-cause mortality in patients with CKD, congestive heart failure, and chronic liver disease.[9] On the other hand, in a study of 616 patients, Hsu et al. [10] evaluated the effect of continuous metformin treatment on renal function in patients with T2DM and moderate CKD (eGFR 30–60 mL/min/1.73 m2). The study group concluded that continuous metformin therapy was associated with a decline in renal function in patients with T2DM and moderate CKD. However, as this was a retrospective study, the authors could not exclude putative confounding factors such as lifestyle, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, cumulative duration of exposure, and defined daily dose of metformin.

Effects of DPP-4 Inhibitor Linagliptin Versus Sulfonylurea Glimepiride as Add-on to Metformin on Renal Physiology in Overweight Patients with Type 2 Diabetes (RENALIS)

A double-blind randomized trial was carried out to compare effects of the dipeptidyl peptidase 4 (DPP-4) inhibitor linagliptin with those of a sulfonylurea on renal physiology in metformin-treated patients with T2D patients. [11]

In this trial, trial, 46 overweight T2D patients without renal impairment received once-daily linagliptin (5 mg) or glimepiride (1 mg) for 8 weeks. Fasting glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were assessed by inulin and para-aminohippuric acid clearances. Fractional excretions, urinary damage markers, and circulating DPP-4 substrates (among others, glucagon-like peptide 1 and stromal cell–derived factor-1a [SDF-1a]) were measured. [11]

HbA1c reductions were similar with linagliptin (–0.45 ± 0.09%) and glimepiride (–0.65 ± 0.10%) after 8 weeks ($P = 0.101$) of treatment. Linagliptin compared to glimepiride did not affect fasting glomerular filtration rate (GFR), effective renal plasma flow (ERPF), estimated intrarenal hemodynamics, or damage markers. Only linagliptin increased fractional excretion (FE) of sodium (FENa) and potassium, without affecting FE of lithium. Linagliptin-induced change in FENa correlated with SDF-1α ($R = 0.660$) but not with other DPP-4 substrates. [11]

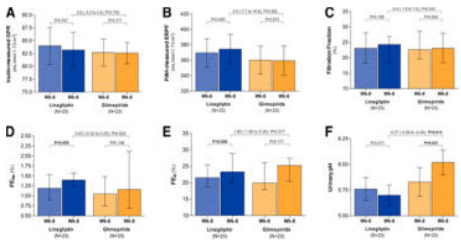

Figure 3 : Renal hemodynamic and tubular effects of linagliptin and glimepiride after 8weeks of treatment. Mean + SEM(A–C and F), median [IQR] (D and E), and baseline-corrected mean difference (95% CI). Multivariable linear regression models were used to examine baseline-corrected linagliptin-induced effects compared with glimepiride. Paired t tests (A–C and F) or Wilcoxon signed rank tests (D and E)were used for within-group comparisons. Significant differences are indicated in boldface type. PAH, para-aminohippuric acid; Wk, week.

Hence, the study reported that linagliptin does not affect fasting renal hemodynamics compared with glimepiride in T2DM patients. DPP-4 inhibition promotes modest natriuresis, possibly mediated by SDF-1a, likely distal to the macula densa. 11

Summary

The effect of linagliptin in T2D patients with CKD has been shown to improve renal progression without significant effect on proteinuria and glucose control. Further, linagliptin can be a new therapeutic option for treating diabetic nephropathy 4 and it also shown to prevent the impairment of renal endothelial function due to hyperglycaemia in type 2 diabetes. [5]

On the other hand, metformin has also appeared to be associated with decreased all-cause mortality in patients with CKD, congestive heart failure, and chronic liver disease. [9]

The RENALIS study has shown linagliptin does not affect fasting renal hemodynamics compared with glimepiride in T2DM patients. DPP-4 inhibition promotes modest natriuresis, possibly mediated by SDF-1a, likely distal to the macula densa. [11]

Therefore, the linegliptin in combination with metformin can be beneficial for renal impaired patients with T2D.

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