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The Renal Protective Effects of Liraglutide in Patients with Type 2 Diabetes and Nephropathy: A Retrospective Observational Study

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Abstract

Background: We conducted a retrospective observational study in type 2 diabetic patients with nephropathy to examine the effects of long-term administration of liraglutide on the improvement of renal function.

Methods: The study included 84 type 2 diabetic patients diagnosed with overt nephropathy (stage 3 or stage 4),in whom at least 1 year had passed since switching treatment to liraglutide. Glycatedhemoglobin (HbA1c), glycoalbumin (GA), body mass index (BMI), estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR) were aggregated, and the values before liraglutide administration (baseline) were compared with those after 6 and 12 months ofliraglutide administration. The rates of change in eGFR (ΔeGFR) over 1 year from baseline to 12 months of liraglutide administration were calculated and compared.

Results: HbA1c and GA were significantly decreased after liraglutide administration compared with baseline. ΔeGFR was significantly improved after liraglutide administration compared with pretreatment. No correlations were observed between rate of ΔeGFR improvement and changes in HbA1c or BMI.

Conclusion: Long-term administration of liraglutide showed renal protective effects in patients with type 2 diabetes presenting with overt nephropathy. These beneficial effects were suggested to direct effects on the kidney, independent of improvements in blood glucose or BMI.

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Introduction

Diabetic nephropathy, together with diabetic peripheral neuropathy and diabetic retinopathy, are the three major complications of type 2 diabetes. Albuminuria is positive in ≥40% of type 2 diabetic patients, and can progress to severe renal failure requiring treatment with dialysis. Diabetic nephropathy is a leading cause of dialysis initiation in Japan, and inhibition of nephropathy progression is an important issue in the treatment of type 2 diabetic patients.

Glucagon-like peptide-1 (GLP-1) is an in cretin hormone that induces insulin secretion from pancreatic beta-cells in a glucose-dependent manner. In addition to its insulin secretion-promoting action, GLP-1 inhibits glucagon secretion, delays gastric emptying, and decreases appetite, thereby exhibiting an overall improvement effect on hyperglycemia [1]. As GLP-1 is usually degraded rapidly by its degradative enzyme dipeptidyl peptidase-4 (DPP-4), its onset of action is quick and its duration of action is short. However, degradation-resistant GLP-1 receptor agonists show not only continuous improvement effects on blood glucose, but also clinical benefits with minimal risks for weight gain or hypoglycemia through their mechanism of action.

In recent years, studies on mice and rats have clarified that GLP-1 receptor agonists bind to GLP-1 receptors in the kidney and have direct renal protective effects through antioxidant, anti-inflammatory, and anti-apoptotic effects [2–5]. However, there have been only a few reports on the renal protective effects of long-term administration of GLP-1 receptor agonists in type 2 diabetic patients. Liraglutide is a GLP-1 receptor agonist that shares high homology (97%) with human GLP-1, and has effects that last for 24 h after once-daily administration owing to its long duration of action. Furthermore, it can be used in combination with all insulin formulations and oral hypoglycemic drugs.

In the present study, we examined the renal protective effects of long-term administration of liraglutide in type 2 diabetic patients with overt nephropathy.

Method

We conducted a retrospective observational study, based on medical records, in 84 type 2 diabetic outpatients with overt nephropathy (stage 3 or stage 4),in whom at least 1 year had passed since switching from their prior diabetes treatment to liraglutide treatment following diet/exercise therapy on an outpatient basis. Prior to using the clinical data, we obtained informed consent from the study patients.

Liraglutide was initiated at a dose of 0.3mg/day, with increasing dosage as appropriate, until eventually liraglutide 0.9mg/day was subcutaneously administered to all patients. Treatment with insulin, α-glucosidase inhibitor, and DPP-4 inhibitor drugs, performed prior to liraglutide treatment, was discontinued. Low-dose biguanide (BG) was discontinued and high-dose BG was reduced or discontinued. In patients treated with antihypertensive agents, the seagents were approved as the combination therapy with liraglutide.

Glycated hemoglobin (HbA1c), glycoalbumin (GA), body mass index (BMI), estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR) were measured before liraglutide

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(baseline) and after 6 and 12 months of liraglutide treatment, and the changes in each variable in all patients were aggregated. Furthermore, the changes in each variable were aggregated for groups with and without insulin treatment at baseline (I group and NI group, respectively).

The rates of change in eGFR (ΔeGFR) over 1 year from baseline to 12 months of liraglutide administration were calculated and compared for individual grade 3 or grade 4 patients.

The study was approved by the institutional review board of the Nakakinen Clinic. All parameters were compared using a paired t-test, and their correlations with the rate of ΔeGFR improvement were examined by Pearson's product–moment correlation coefficient. Correlation were determined to be significant for values of $p<0.05$.

Results

Eighty-fourtype 2 diabetic patients diagnosed with overt nephropathywere included in the study. There were 65 males and 19 females and the mean age was 63.5 ± 11.5 years. At baseline, HbA1c was 7.97 ± 1.69%, GA was 21.68 ± 5.39%, and BMI was 25.62 ± 3.63kg/m2. Baseline eGFR (mL/min/1.73m2) was 48.69 ± 27.24,comprising 28 patients with GFR of ≥60, 27 patients with eGFR of 30–60, and 29 patients with eGFR of<30. Regarding severity of nephropathy, 55 patients were stage 3 and 29 were stage 4. Diabetes treatment before start of liraglutide treatment was insulin therapy in 50 patients (I group) and non-insulin therapy in 34 patients (NI group).

Table 1 shows the effects of administration of liraglutide on HbA1c, GA, BMI, eGFR, and UACR. Overall (stage 3/4 patients), compared with baseline, HbA1c was significantly decreased after 6 months (7.49 ± 1.66%, $p<0.001$) and 12 months (7.38 ± 1.35%, $p<0.01$) of liraglutide administration. Also compared with baseline, GA was significantly decreased at 6 months (20.65 ± 5.76%, $p<0.05$) and remained decreased at 12 months, albeit not significantly (20.67 ± 5.15%). These tendencies were also observed in patients with stage 3.In the I group, HbA1c and GA were 7.43±1.72% and 20.34±4.92% at baseline, 7.27 ± 1.78% and 20.12±5.43% at 6 months, and 7.02±1.31%, and 20.32±4.96% at 12 months, respectively, with no significant decreases observed. Meanwhile, in the NI group, HbA1c was 8.81±1.26% at baseline, 7.82±1.39% at 6 months, and 7.90±1.23% at 12 months, with a significant decrease observed at 6 months. In the NI group, GA was 23.75±5.42% at baseline, 21.45 ±6.13% at 6 months, and 21.17 ±5.78% at 12 months, with significant decreases at both 6 and 12 months.

Overall or individual stage3 or stage 4 patients, no change in BMI from baseline was observed after 6 and 12 months of liraglutide administration (Table 1).However, in the I group, significant decreases were observed, being 25.43 ± 3.21kg/m^2 at baseline, 24.97±3.31kg/m^2 at 6 months, and 24.39±2.87kg/m^2 at 12 months. In the NI group, no significant decreases were observed, being25.92 ± 4.18kg/m^2 at baseline, 25.81±4.43kg/m^2 at 6 months, and 25.13 ± 4.32kg/m^2 at 12 months.

In stage 3 patients, UACR (g/g creatinine) was 978.7±1851.8 at baseline, and significantly decreased to 922.4±1311.2 at 12 months ($P<0.05$) (Table 1). In stage 3/4 patients, compared with baseline, eGFR (mL/min/1.73m2) was significantly decreased to 43.34±23.11 at 6 months ($p<0.05$) and 45.16±25.44 at 12 months ($p<0.01$) (Table 1). These changes in indicators of kidney function were also observed in patients with stage 3.Comparisons of the rates of change in eGFR (ΔeGFR;mL/min/1.73m2/year) over 1 year from baselineto 12 months of administration revealed significant improvements from −5.63±7.25 to −0.27±8.95 in stage 3 patients ($p< 0.01$) and from −7.92±6.37 to −0.09±5.03in stage 4 patients ($p< 0.001$) (Figure 1).

	Baseline	6 months	12 months
Stage 3/4	(n = 84)	(n = 84)	(n = 63)
HbA1c(%)	7.97±1.69	7.49±1.66***	7.38±1.35**
GA(%)	21.68±5.39	20.65±5.76*	20.67±5.15
BMI(kg/m^2)	25.62±3.63	25.30±3.81	24.69±3.56
eGFR(mL/min/1.73m^2)	48.69±27.24	43.34±23.11*	45.16±25.44**
UACR(g/g creatinine)†	978.7±1851.8††	830.7±1749.7††	922.4±1311.2†††*
Stage 3	(n = 55)	(n = 55)	(n =42)
HbA1c (%)	8.23±1.79	7.78±1.83**	7.52±1.48*
GA (%)	21.28±5.83	20.54±6.67*	20.41±5.71
BMI (kg/m2)	25.95±3.68	25.62±3.78	24.98±3.73
eGFR (mL/min/1.73 m^2)	63.57±21.77	56.30±18.59**	57.81±21.50**
UACR (g/g creatinine)	978.7±1851.8	830.7±1749.7	922.4±1311.2*
Stage 4	(n = 29)	(n = 29)	(n = 21)
HbA1c (%)	7.47±1.35	6.94±1.10**	7.12±0.98
GA (%)	21.81±4.40	20.85±3.44	21.20±3.72
BMI (kg/m^2)	25.61±3.45	24.68±3.80	24.13±3.10
eGFR (mL/min/1.73 m^2)	20.46±5.81	21.45±9.48	19.85±7.50

Table 1: Changes in variables from baseline to 6 and 12 months.
†Data are stage 3 patients only. ††n=55. †††n=42.
HbA1c, glycated hemoglobin; GA, glycoalbumin; BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.Data are expressed as mean ± standard deviation.*$p< 0.05$, **$p< 0.01$, ***$p< 0.001$,significantdifference for mean change from baseline.

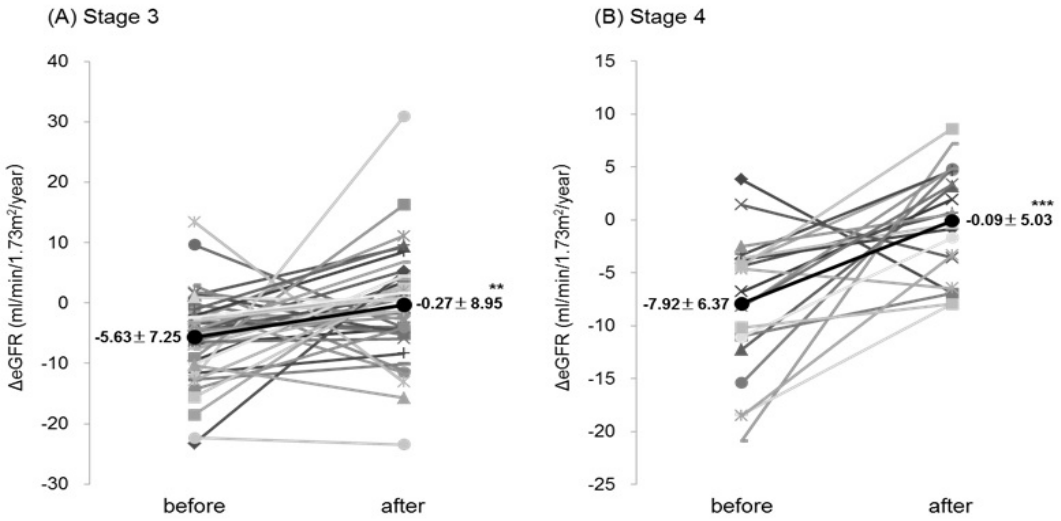

Figure 1: Rates of change in estimated glomerular filtration rate (ΔeGFR; mL/min/1.73 m2/year) before and after administration of liraglutide for 12 months in type 2 diabetic patients with stage 3 (A; n=42)and stage 4 (B; n=21) diabetic nephropathy. The closed circles (•) indicate the mean ± SD. **p< 0.01, ***p< 0.001,significantdifference for mean change from baseline.

The rates of ΔeGFR improvement were 4.21±10.84 in males, 8.25 ±9.55 in females, 5.86±10.91 in the I group, and 4.10±10.05 in the NI group, with no significant differences observed for sex or presence/absence of prior insulin treatment. Moreover, no significant correlations were observed between the rates of ΔeGFR improvement and age, changes in HbA1c (r = 0.240), or changes in BMI (r = 0.096).

Discussion

Unlike other GLP-1 receptor agonists, the pharmacokinetics of liraglutide is known to be unaffected by renal dysfunction, because liraglutide is not excreted from the kidney [6,7].Therefore, enhanced hypoglycemic action and increased adverse events are not observed in type 2diabetic patients complicated with renal dysfunction, and there is the advantage that treatment can be performed without dose adjustment [8,9]. A significant improvement in blood glucose was observed after long-term administration of liraglutide in type 2 diabetic patients with nephropathy in the present study.

When focusing on the types of therapy before liraglutide treatment, I group showed a significant decrease in BMI after the start of liraglutide treatment, but no significant changes in HbA1c or GA. Although no further improvement in glycemic control maybe achieved, improved physical condition by weight loss can be expected after switching insulin treatment to liraglutide treatment.

A significant decrease in UACR was observed compared with baseline in grade 3 patients. Although the data were not shown, this decrease was particularly marked in the NI group. Because HbA1c remained unchanged in the I group but was decreased in the NI group in this study, the decrease in UACR was considered to have been caused by the improvement in glycemic control, rather than by the direct action of liraglutide. Furthermore, in grade 3 patients, eGFR was significantly decreased compared with baseline. This was considered to reflecta change associated with the progression of nephropathy. In fact, calculation of ΔeGFR before the start of liraglutide administration showed a significant decrease in eGFR. In addition, this decrease in eGFR was observed not only in patients with more severe stage 3 nephropathy, but also in patients with stage 4 nephropathy, and progression of nephropathy before the start of liraglutide administration was indicated in both groups. However, calculation of ΔeGFR after liraglutide administration revealed that the changes were slight and the decreases were significant compared with baseline, suggesting that the reduced renal function was being significantly inhibited. Liraglutide is considered effective for preventing reduced renal function, i.e., progression of nephropathy, and it became clear that liraglutide exerted a renal protective effect in patients with more severe nephropathy, based on the significant effects observed in not only stage 3 patients, but also stage 4 patients. It is considered that liraglutide can delay the transition to dialysis associated with reduced renal function in type 2 diabetic patients as much as possible. As no correlations were observed between the rates of ΔeGFR improvement and changes in HbA1c or BMI, it was suggested that the renal protective effect of liraglutide was not an effect associated with improved blood glucose or reduced BMI, but an effect with a different underlying mechanism.

Expression of GLP-1 receptors in the kidney has been confirmed. In the rat kidney, GLP-1 receptors are localized in the glomerular endothelium and proximal convoluted tubules [2,10],while in the human and monkey kidney, GLP-1 receptors are highly expressed in the smooth muscle cells of arterioles [11]. The potential for increases in eGFR in rats via activation of intracellular pathways through cyclic AMP and protein kinase A was reported [10]. It is possible that the renal protective effect of liraglutide observed in the present study may have been induced by a similar mechanism.

In a similar study on the beneficial effect of ΔeGFR with liraglutide treatment in Japanese diabetic patients with overt nephropathy [12], angiotensin-receptor blockers (ARB) was concomitantly used as an antihypertensive agent in all patients and the renal protective effect of liraglutide was considered to be exhibited under renin-angiotensin system suppression. In this study, the use of antihypertensive agents, such as ARB or angiotensin-converting enzyme inhibitors (ACEi), was approved; there is a possibility that these agents have influenced renal protective action.

Furthermore, the effects of liraglutide on the kidney were considered to be related to decreases in HbA1c and BMI, being different from the present study. In a study in which liraglutide was administered at higher doses (1.2–1.8mg/day) than in the present study, the following results were seen: eGFR was significantly increased after 12 months of liraglutide administration in patients with renal dysfunction; the eGFR levels in some patients reached the normal range [13]; and the improvement in eGFR was considered to be a direct effect of liraglutide on the kidney because it was independent of the improvement in blood glucose.

In type 2 diabetic patients with overt nephropathy, it is desirable to maintain good glycemic control while affording renal protection. In the present observational study, liraglutide was found to be a hypoglycemic agent with renal protective effects. Further verification of its usefulness is needed through larger-scale prospective studies in the future.

Conclusion

In conclusion, the present study confirmed the improvement in ΔeGFR, independent of improvement in blood glucose or decrease in BMI, after long-term liraglutide administration in type 2 diabetic Japanese patients with overt nephropathy. Liraglutide, a GLP-1 receptor agonist, was suggested to have a renal protective effect from early nephropathy throughout the conservative stage of chronic renal failure by improvement in blood glucose, weight loss, or direct GLP-1 effect.

Competing Interests

All of the authors, except A. Tamasawa and T. Osonoi, report they have no conflicts of interest to disclose. A. Tamasawa and T. Osonoi received honoraria and travel expenses for lectures at an event organized by Novo Nordisk.

Author Contributions

All authors contributed equally to this work. All authors contributed substantially to the study conception and design, as well as to data acquisition and interpretation, and drafting of the manuscript.

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