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The Glucagon-Like Peptide-1 Receptor Agonist, Liraglutide, Attenuates the Progression of Overt Diabetic Nephropathy in Type 2 Diabetic Patients

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Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. Glucagon-like peptide-1 (GLP-1) is one of the incretins, gut hormones released from the intestine in response to food intake. GLP-1 receptor (GLP-1R) agonists have been used to treat type 2 diabetes. Here, we studied the effect of the administration of a GLP-1R agonist, liraglutide, on proteinuria and the progression of overt DN in type 2 diabetic patients. Twenty-three type 2 diabetic patients with overt DN, who had already been treated with blockade of renin-angiotensin system under dietary sodium restriction, were given liraglutide for a period of 12 months. Treatment with liraglutide caused a significant decrease in HbA1c from 7.4 ± 0.2% to 6.9 ± 0.3% (p = 0.04), and in body mass index (BMI) from 27.6 ± 0.9 kg/m^2 to 26.5 ± 0.8 kg/m^2 after 12 months (p < 0.001), while systolic blood pressure did not change. The progression of DN was determined as the rate of decline in estimated glomerular filtration rate (eGFR). The 12-month administration of liraglutide caused a significant decrease in proteinuria from 2.53 ± 0.48 g/g creatinine to 1.47 ± 0.28 g/g creatinine (p = 0.002). The administration of liraglutide also substantially diminished the rate of decline in eGFR from 6.6 ± 1.5 mL/min/1.73 m^2/year to 0.3 ± 1.9 mL/min/1.73 m^2/year (p = 0.003). Liraglutide can be used not only for reducing HbA1c and BMI, but also for attenuating the progression of nephropathy in type 2 diabetic patients.

Keywords: diabetic nephropathy; extra-pancreatic actions; glucagon-like peptide-1 receptor agonist; liraglutide; overt proteinuria

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Introduction

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. DN is a clinical syndrome characterized by proteinuria, hypertension, and a relentless decline in glomerular filtration rate (GFR). Several therapeutic approaches have been performed to reduce proteinuria and to retard the decline in GFR in patients with DN. Although the introduction of antihypertensive therapy by the blockade of the renin-angiotensin system (RAS) with either angiotensin-converting enzyme inhibitor (ACEI)s or angiotensin II receptor blocker (ARB)s reduced proteinuria and improved the rate of decline in GFR in DN, the mean rate of decline in GFR still remains at 2.0-10 ml/min/year (Björck et al. 1992; Lewis E et al. 1993; Elving el al. 1994; Tarnow et al. 2000).

Glucagon-like peptide-1 (GLP-1) is one of the incretins, gut hormones secreted from L cells in the intestine in response to food intake. GLP-1 augments glucose-induced insulin release from pancreatic β-cells, suppresses glucagon secretion, and slows gastric emptying (Kim and Egan 2008). Therefore, GLP-1 has been proposed as a potential therapeutic target for the treatment of patients with type 2 diabetes mellitus. The biological actions of GLP-1 on pancreatic cells are mainly mediated by the high-affinity GLP-1 receptor (GLP-1R) (Winzell and Ahrén 2007). GLP-1R is expressed not only in the pancreas, gut and hypothalamus, but also in the kidney (Bullock et al. 1996).

Liraglutide is a long-acting human GLP-1 analog that has a high degree of homology to native GLP-1 (Elbrønd et al. 2002). GLP-1R agonists, such as exendin-4 and liraglutide, are new therapy options for type 2 diabetes, and produced substantial and clinically significant reductions in HbA1c and fasting and postprandial glucose levels with moderate weight loss (Nauck et al. 2009).

With respect to the effects of GLP-1 on the kidney, it has been reported that in animal model, GLP-1R agonists have various extra-pancreatic actions such as regulating sodium excretion in the tubular cells of the kidney (Hirata et al. 2009) and they have been shown to directly prevent the progression of DN through the suppression of inflammatory process via the activation of GLP-1R in kidney tis-

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sue (Kodera et al. 2011).

Furthermore, GLP-1 is rapidly degraded in the body by dipeptidylpeptidase (DPP) IV. DPP IV inhibitor works by inhibiting the DPP IV enzyme that degrades GLP-1, thereby stabilizing the intact active form of GLP-1. DPP IV inhibitors are one of the latest therapeutic classes of glucose-lowering medications. Liu et al. (2012) reported that the increase in endogenous incretine induced by DPP IV inhibitor reduced proteinuria and improved creatinine clearance through the activation of the GLP-1R in diabetic animal model. Therefore, GLP-1 is of potential interest as a possible therapeutic regimen for treatment of DN in human. The present study was performed to clarify whether a GLP-1R agonist, liraglutide, could reduce proteinuria and attenuate the progression of overt DN in type 2 diabetic patients.

Methods

Among a population of 1,220 type 2 diabetic patients who regularly visited the out-patient diabetic unit of our hospital between March 2008 and September 2010, 23 patients who had diabetic retinopathy or diabetes for more than 10 years, were enrolled in the present study. They had signs of overt DN even after 4-month treatment with oral hypoglycemic agents and/or insulin, diet therapy including salt restriction (6 g/day) and blood pressure control by the administration of antihypertensive drugs including ARBs. Overt DN was defined as in terms of proteinuria greater than 0.5 g/g creatinine (g/gCr) in at least three urine samples, in the absence of urinary tract infection. Patients with type 1 diabetes or other types of renal disease were excluded. Liraglutide was administered over 12 months. Liraglutide was subcutaneously injected once daily at the same time each day in the abdomen or thigh using a pre-filled pen device. Liraglutide 0.3 mg a day was started as an initial dose and followed with weekly increment of 0.3 mg, up to 0.9 mg by the end of the third week. During the period of liraglutide administration, no further diet therapy and no additional administration of antihypertensive drugs were done.

The value for HbA1c (%) is estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value. The estimated GFR (eGFR) was calculated using the following equation, as recommended by Japanese Society for Nephrology: eGFR (mL/min/1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female) (Lamb et al. 2005; Retnakaran et al. 2006; Matsuo et al. 2009). The eGFRs were measured every 2 months for 1 through 3 years before the administration of liraglutide and every month during the administration. The rates of change in eGFR (mL/min/1.73 m^2/year) before and after the administration of liraglutide were calculated by linear regression analysis on all eGFR values in each subject before the administration of liraglutide and during the administration, respectively. Correlations were calculated as Spearman correlation coefficients.

The study was approved by the ethics committee of Chiba Prefectural Togane Hospital and was conducted in accordance with the Helsinki declaration. Informed consent was obtained from all subjects.

Statistical analysis

Statistical analysis was performed using the JMP® 9 software (SAS Institute Inc., Cary, NC, USA). Differences between before and after the administration of liraglutide were examined for statistical significance using paired *t*-test. All values are expressed as the means ± SEM. Values of $p < 0.05$ were considered to indicate statistically significant differences.

Results

In the present study, 23 type 2 diabetic patients with overt DN (male: 13 and female: 10, mean age 58.2 ± 2.3 years) were included. Baseline medication for diabetes are as follows: biguanide: $n = 10$, α-glucosidase inhibitors: $n = 5$, glinides: $n = 4$, and insulin: $n = 18$. All patients received ARBs: olmesartan (40 mg/day): $n = 20$, telmisartan (80 mg/day) $n = 1$, and valsartan (160 mg/day) $n = 2$. ACEI: $n = 4$. Ca channel blocker: $n = 23$, α-blocker: $n = 3$, and central sympatholytic agent: $n = 1$. Administration of liraglutide caused a significant decrease in HbA1c levels from 7.4 ± 0.22% (57.6 ± 2.4 mmol/mol) to 7.0 ± 0.22% (53.4 ± 2.4 mmol/mol) after 1 month of administration ($p < 0.001$), to 6.9 ± 0.25% (51.8 ± 2.7 mmol/mol) after 12 months ($p = 0.035$). Also, BMI were significantly decreased from 27.6 ± 0.9 kg/m^2 to 27.2 ± 0.8 kg/m^2 after 1 month of administration of liraglutide ($p < 0.001$), to 26.5 ± 0.8 kg/m^2 after 12 months ($p < 0.001$). Systolic blood pressure (SBP) did not significantly change between before and after the administration of liraglutide. Proteinuria was significantly decreased from 2.53 ± 0.48 g/gCr to 1.62 ± 0.31 g/gCr after 1 month ($p < 0.001$), to 1.47 ± 0.28 g/gCr after 12 months ($p = 0.0015$) (Table 1). There were no significant differences between proteinuria in 1, 6 and 12 months.

A strong correlation was observed between baseline proteinuria and changes in proteinuria after 12-month administration of liraglutide ($r = 0.84$, $p < 0.0001$) (Fig. 1). The administration of liraglutide also substantially diminished the rate of decline in eGFR from 6.6 ± 1.5 mL/min/1.73 m^2/year to 0.3 ± 1.9 mL/min/1.73 m^2/year ($p = 0.003$) (Fig. 2). During this study, there were no major adverse events including major hypoglycemic events. No sex difference was observed in the changes in proteinuria and the rate of change in eGFR after 12 months administration of liraglutide (Figs. 1 and 2).

Discussion

The present study was performed to clarify whether GLP-1R agonist could have a renoprotective effect in type 2 diabetic patients who had overt DN even after 4-month treatment with maximal doses of ARBs under dietary sodium restriction.

Proteinuria is an established and modifiable progression promoter (Hovind et al. 2001), and intervention targeting this factor has been the most successful renoprotective treatment in DN. In the present study, administration of liraglutide caused a significant decrease in proteinuria concomitant with significant reductions in both of HbA1c levels and BMI, while SBP did not change. It is well known that glycemic control induces a significant decrease in pro-

Table 1. Effect of 12-month administration of liraglutide on HbA1c, BMI, SBP, eGFR and proteinuria in type 2 diabetic patients (n = 23).

	Before	1 month	6 months	12 months
HbA1c (%)	7.4 ± 0.22	7.0 ± 0.22***	6.6 ± 0.25***	6.9 ± 0.25*
BMI (kg/m^2)	27.6 ± 0.9	27.2 ± 0.8***	26.2 ± 0.8****	26.5 ± 0.8***
SBP (mmHg)	140.2 ± 3.1	135.6 ± 2.7	135.3 ± 2.8	137.1 ± 2.9
Alb (g/dl)	4.06 ± 0.12	4.16 ± 0.19	4.11 ± 0.11	4.10 ± 0.13
eGFR (mL/min/1.73 m^2)	58.2 ± 6.4	57.1 ± 6.7	58.8 ± 6.6	56.9 ± 6.9
urinary protein (g/g creatinine)	2.53 ± 0.48	1.62 ± 0.31***	1.45 ± 0.30***	1.47 ± 0.28**

HbAlc, hemoglobin Ale; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure; Alb, serum albumin; eGFR, estimated glomerular filtration rate.

All values are expressed as the means ± SEM unless otherwise indicated. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

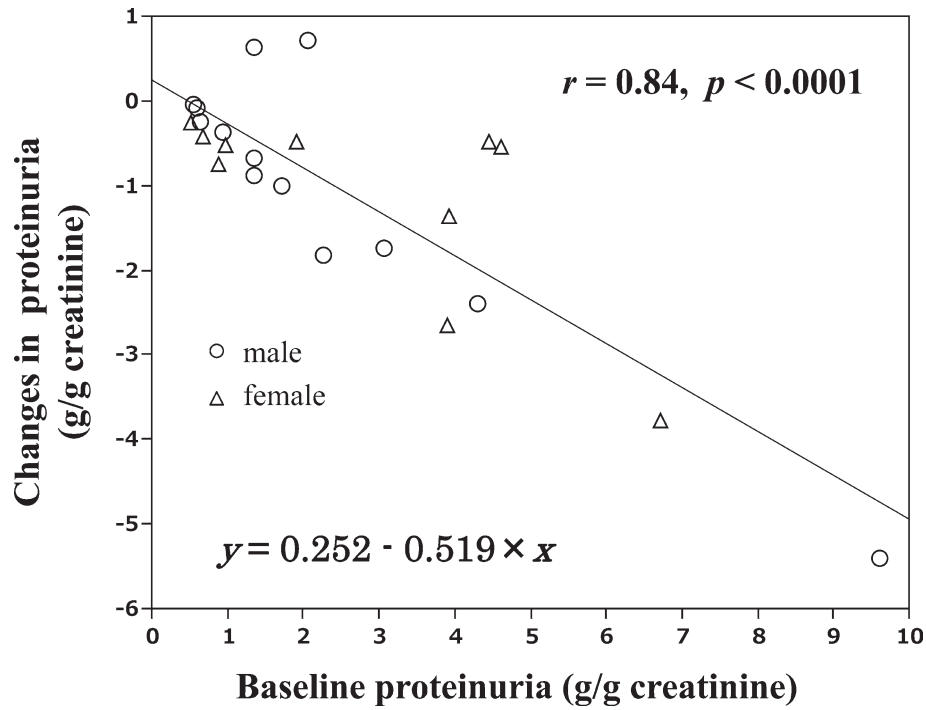

Fig. 1. Relationship of baseline proteinuria and changes in proteinuria.
Shown is the relationship of baseline proteinuria and changes in proteinuria after 12 months administration of liraglutide in type 2 diabetic patients with diabetic nephropathy (n = 23). Changes are expressed as values of positive or negative change with respect to baseline values. ○: male, △: female.

teinuria in type 2 DN (UK Prospective Diabetes Study Group. 1998). Also moderate weight reduction in overweight diabetic patients with overt DN induces a significant decrease in proteinuria (Saiki et al. 2005). The reduction in HbA1c levels and BMI after the administration of liraglutide may contribute to antiproteinuric effect of GLP-1R agonists observed in the present study.

Ninomiya et al. (2009) reported that high albuminuria and low eGFR are independent risk factors for renal events among patients with type 2 diabetes. A reduction in proteinuria shortly after onset of antihypertensive therapy by the blockade of the RAS is the best predictor of long-term preservation of renal function (Rossing et al. 1994; Breyer et al. 1996). It seems to be worthwhile that a significant reduction in proteinuria was observed shortly after the administration of liraglutide such as within one month (Table 1).

The rate of decline in GFR has been one of the primary endpoints in clinical trials of DN, whereas a reduction in urinary protein excretion has been considered a surrogate endpoint, a predictor of a beneficial outcome (Rossing et al. 1994; Breyer et al. 1996). In randomized controlled trials, the rate of decline in GFR in overt DN is 2-10 ml/min/year after the introduction of antihypertensive therapy with blockade of the RAS (Björck et al. 1992; Lewis E et al. 1993; Elving el al. 1994; Tarnow et al. 2000). All patients

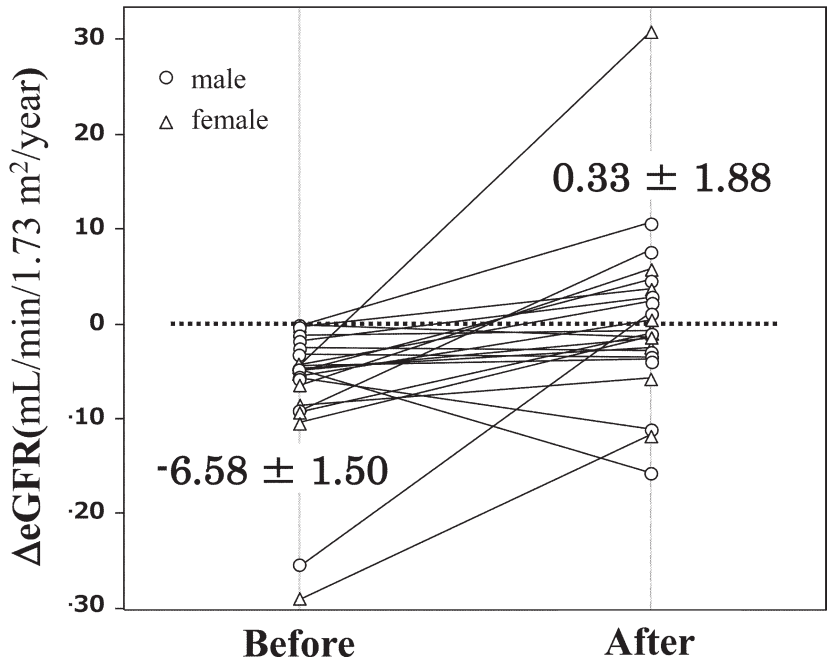

Fig. 2. Effect of 12-month administration of liraglutide on the rates of change in eGFR.
Shown are the rates of change in estimated glomerular filtration rate (eGFR) (ΔeGFR; mL/min/1.73 m^2/year) before and after 12 months administration of liraglutide in type 2 diabetic patients with diabetic nephropathy (n = 23). means ± SEM, $p < 0.01$. ○: male, △: female.

in the present study had been treated under the blockade of the RAS over 4 months before the administration of liraglutide. In our study, the mean rate of decline in eGFR before the administration of liraglutide (6.6 mL/min/1.73 m^2/year) was similar with those described in the earlier reports (Björck et al. 1992; Lewis E et al. 1993; Elving el al. 1994; Tarnow et al. 2000). It seems to be valid to evaluate the effects of liraglutide on the progression of overt DN among the patients who were included in the present study. For the long-term evaluation of decline in eGFR, a minimal observation period of 12 months was required (Tarnow et al. 2000). After 12-month administration of liraglutide, the rate of decline in eGFR was substantially diminished from 6.6 mL/min/1.73 m^2/year to 0.3 mL/min/1.73 m^2/year (p = 0.003).

Renoprotective effect of GLP-1R agonists through the direct action on the kidney was first reported in an animal model (Kodera et al. 2011). Ishibashi et al. (2011) also reported that GLP-1R agonist directly acts on mesangial cells via GLP-1R and that it could work as an anti-inflammatory agent via activation of cyclic adenosine monophosphate pathway. A GLP-1R agonist has been shown to attenuate the actions of angiotensin II (Hirata et al. 2009), resulting in an antihypertensive effect in salt-sensitive mice and a reduction in proteinuria, and renal pathology (Yu et al. 2003). This has also been shown with the exanetide analogue AC3174 in Dahl salt-sensitive rats (Liu et al. 2010), where it attenuated hypertension, insulin resistance and renal dysfunction. These actions of GLP-1R agonists on the kidney as mentioned above may contribute to renoprotective effect of liraglutide observed in the present human study.

In the previous study with an animal model, GLP-1R agonists were administered without the blockade of the RAS and exerted renoprotective effects (Kodera et al. 2011). The present study was performed under the combination with the blockade of the RAS. The patients, who had continued overt proteinuria even after 4 months administration of ARBs with dietary salt restriction, were included in the present study. Mima et al. (2012) reported that the renoprotective effects of GLP-1 in animal model were mediated via the inhibition of angiotensin II actions on cRaf (Ser259) and diminished by diabetes because of protein kinase Cβ activation and the increased degradation of GLP-1R in the glomerular endothelial cells. Thus, the renoprotective effect of liraglutide in human DN might be optimized by the combination with the blockade of the RAS.

Recently, Lind et al. (2012) reported that liraglutide combined with insulin therapy is well tolerated for type 2 diabetes, providing significant improvement in glycemic control. Liraglutide combined with insulin therapy has not been covered by Japanese health insurance system. However, clinical trials for evaluating the combination of liraglutide and insulin therapy are now ongoing in Japan.

Although the main limitation of the present study is that the population and the period were limited and the study lacks a control group, our exploratory findings indicate first the possible role of GLP-1R agonists as a potential therapeutic agent for DN in human.

In conclusion, the present study suggests that GLP-1R agonists can be used not only for reducing HbA1c and BMI, but also for attenuating the progression of nephropathy in type 2 diabetic patients.

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Conflict of Interest

The authors declare no conflict of interest.

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