

## 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  $7.4 \pm 0.2\%$  to  $6.9 \pm 0.3\%$  ( $p = 0.04$ ), and in body mass index (BMI) from  $27.6 \pm 0.9 \text{ kg/m}^2$  to  $26.5 \pm 0.8 \text{ kg/m}^2$  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  $2.53 \pm 0.48 \text{ g/g creatinine}$  to  $1.47 \pm 0.28 \text{ g/g creatinine}$  ( $p = 0.002$ ). The administration of liraglutide also substantially diminished the rate of decline in eGFR from  $6.6 \pm 1.5 \text{ mL/min/1.73 m}^2/\text{year}$  to  $0.33 \pm 1.9 \text{ mL/min/1.73 m}^2/\text{year}$  ( $p = 0.003$ ). 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

Tohoku J. Exp. Med., 2013 September, 231 (1), 57-61. © 2013 Tohoku University Medical Press

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

HbA1c, hemoglobin A1c; 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  $\pm$  SEM unless otherwise indicated.  $^*p < 0.05$ ,  $^{**}p < 0.01$ ,  $^{***}p < 0.001$ ,  $^{****}p < 0.0001$ .

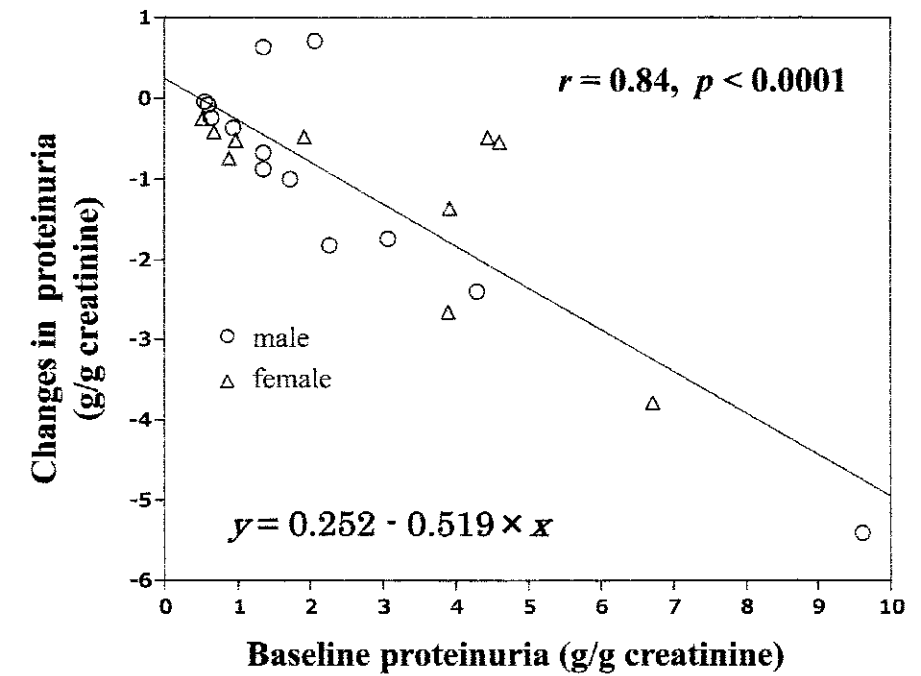


Fig. 1. Relationship of baseline proteinuria and changes in proteinuria. Shown is the relationship of baseline proteinuria and changes in proteinuria after 12 months administration of liraglutide in type 2 diabetic patients with diabetic nephropathy ( $n = 23$ ). Changes are expressed as values of positive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

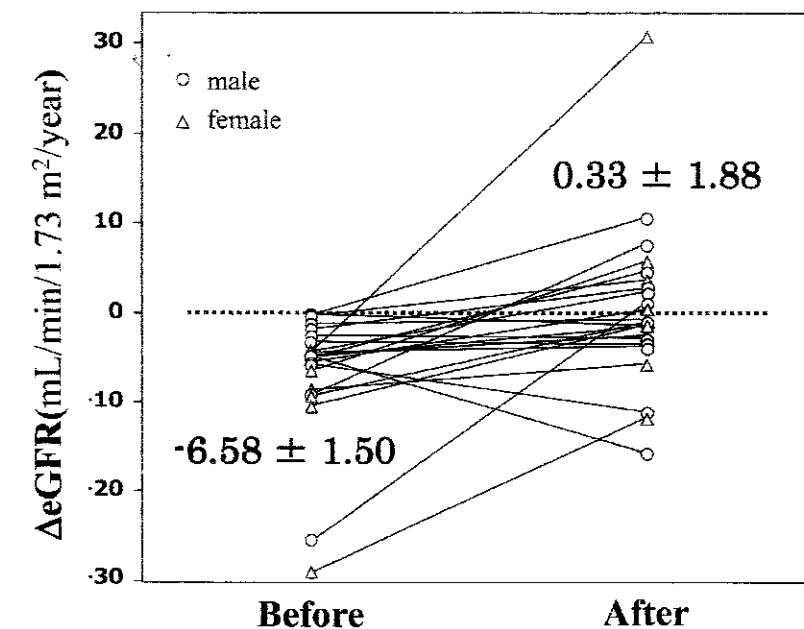


Fig. 2. Effect of 12-month administration of liraglutide on the rates of change in eGFR. Shown are the rates of change in estimated glomerular filtration rate (eGFR) ( $\Delta\text{eGFR}$ ;  $\text{mL/min/1.73 m}^2/\text{year}$ ) before and after 12 months administration of liraglutide in type 2 diabetic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