A novel therapeutic use of Glucagon-like peptide1 receptor agonist for the treatment of overt diabetic nephropathy in patients with type 2 diabetes

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Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide. Proteinuria should be considered a risk marker for progressive loss of renal function in type 2 diabetes with nephropathy, as well as a target for therapy. The predictive power of proteinuria (>0.5g/day) for progressive renal insufficiency has been previously demonstrated in patients with DN. Several therapeutic options are available to reduce proteinuria. Interruption of the renin-angiotensin system with either angiotensinconverting enzyme inhibitor (ACEI)s or angiotensin II receptor blocker (ARB)s is frequently used. By a preclinical animal study, glucagon-like peptide-1 receptor (GLP-1R) agonists directly prevent progress of DN in early stage with GLP-1R in kidney tissue. Although beneficial effects of GLP-1R agonist on lowering blood glucose and reduction of body weight have been established, the effect of GLP-1R agonists on proteinuria in type 2 diabetic patients has not been reported. Therefore we studied if GLP-1R agonist could decrease proteinuria in 21 type 2 diabetic patients (male: 12 and female: 9) with overt DN who were already treated with combining dietary sodium restriction (6g/day) and blockade of renin-angiotensin system. Liraglutide 0.3mg s.c a day was started as an initial dose and followed with weekly increment of 0.3mg, up to 0.9mg by the end of the third week. After 5 months study period, HbA1c and BMI were significantly decreased from 7.0% to 6.4% (p<0.01), and 27.6 kg/m2 to 26.4 kg/m2 (p<0.01), respectively, while there were no significant changes in systolic blood pressure and estimated glomerular filtration rate. Urinary protein to creatinine ratio was significantly decreased from 2.30 g/g to 1.27 g/g (p<0.001). To our knowledge, the present study suggests for first time that the use of liraglutide to overt DN in type 2 diabetic patients is associated with a reduction of proteinuria.

Introduction

During the past two decades, substantial improvements have been achieved in the treatment of diabetic nephropathy (DN) through the introduction of antihypertensive agents blocking renin-angiotensin system(RAS) with angiotensin II antagonist(ARB)s and angiotensin-converting enzyme inhibitor(ACEI)s. [1,2)]

DN is the leading cause of end-stage renal disease worldwide, therefore the therapy for DN is important even now.

We investigated whether the use of Glucagon-Like Peptide 1 Receptor (GLP-1R) agonist to type 2 diabetic patients with overt proteinuria (>0.5g/g creatinine) is associated with a reduction of proteinuria.

Materials and Methods

1. Subjects:

We selected 21 patients from the patients with overt type 2 diabetic nephropathy (DN) who underwent regular follow-up at our hospital depend on the period of treatment for blood sugar and blood pressure control and salt restriction.

2. Study design

Liraglutide 0.3mg s.c a day was started as an initial dose and followed with weekly increment of 0.3mg, up to 0.9mg by the end of the third week. Reduction of baseline medication for diabetes was allowed after randomisation if necessitated by hypoglycemia. During study period, no further diet therapy and no additional administration of antihypertensive drugs were done. The doses of antihypertensive drugs remained unchanged.

3. 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.

Discussion

1. GLP-1R is produced not only in the pancreas, gut and hypothalamus, but also in the kidney.[3)]
2. GLP-1R agonists have various extra-pancreatic actions such as regulating sodium excretion in the tubular cells of the kidney.[4)]
3. Kodera et al first demonstrated that GLP-1R agonists directly improve proteinuria in animal model of diabetes and prevent DN via an anti-inflammatory action without lowering blood glucose level.[5)]
4. Ishibashi et al 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.[6)]

Conclusion

Our study has shown that the use of liraglutide to overt DN in type 2 diabetic patients is associated with as reduction of proteinuria.

Results

Effect of 6 months administration of liragultide on HbA1c, BMI, SBP, eGFR and proteinuria in Type 2 diabetic patients

whole patients (n = 21)

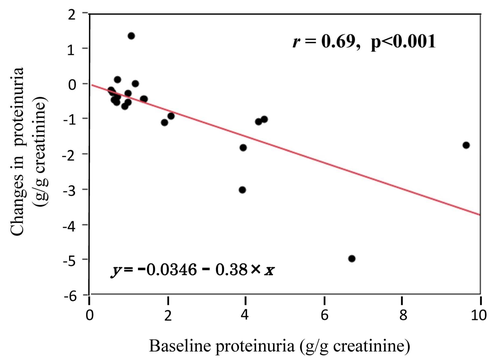
	Before	1 month	3 months	6 months
HbA1c (%)	7.50 ± 0.23	7.07 ± 0.24***	6.80 ± 0.24**	6.77 ± 0.26**
BMI (kg/m²)	28.0 ± 0.85	27.4 ± 0.85***	26.6 ± 0.78**	26.6 ± 0.79***
SBP (mmHg)	135.9 ± 2.8	136.7 ± 2.8	136.0 ± 3.0	136.0 ± 3.1
eGFR (ml/min/1.73m²)	60.3 ± 6.3	61.1 ± 7.0	59.8 ± 6.6	62.2 ± 6.7
urinary protein (g/g creatinine)	2.32 ± 0.52	1.55 ± 0.34**	1.33 ± 0.33***	1.46 ± 0.38**

patients whose HbA1c change were less than 0.5% during 6 months study period (n = 7)

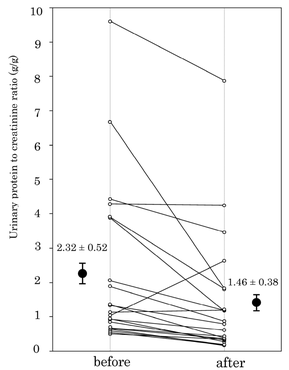
	Before	1 month	3 months	6 months
HbA1c (%)	7.39 ± 0.41	7.33 ± 0.46	7.57 ± 0.52	7.21 ± 0.60
BMI (kg/m²)	28.1 ± 0.98	27.7 ± 0.98	27.3 ± 1.02*	27.1 ± 0.97**
SBP (mmHg)	134.3 ± 4.9	138.9 ± 6.1	144.1 ± 6.0	132.9 ± 4.3
eGFR (ml/min/1.73m²)	63.1 ± 7.4	61.6 ± 6.9	61.5 ± 8.2	67.8 ± 8.3
urinary protein (g/g creatinine)	1.00 ± 0.21	0.77 ± 0.23*	0.55 ± 0.12*	0.62 ± 0.14*

HbA1c(NGSP) *:p<0.05, **<0.01, ***:p<0.001

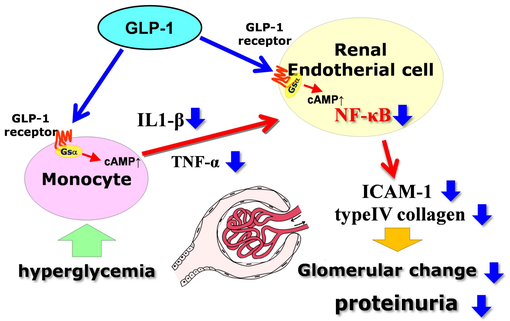
Relationship of baseline proteinuria and changes in proteinuria after 6 months administration of liraglutide



Changes in urinary protein to creatinine ratio before and after 3 months administration of liraglutide in type 2 diabetic patients with diabetic nephropathy



Molecular mechanism of nephroprotective effects of GLP-1



Ref:Kodera R, Shikata K, Kataoka HU et al. [5)] and Ishibashi Y, Nishino Y, Matsui T, Takeuchi M, Yamagishi S [6)]

【Acknowlegments】

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