THE EFFICACY OF TREATMENT WITH GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN CHRONIC DIALYSIS PATIENTS WITH DIABETES MELLITUS

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Introduction

- Many patients on renal replacement therapy suffer from diabetes mellitus (DM). But most oral antidiabetic agents have limitations in patients (pts) with CKD.
- **Elderly patients with DM and CKD are at particular risk of hypoglycemia.** [1)]Incretin-based therapies , glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, possess a potent antihyperglicemic effect with a low risk of hypoglycemia.
- GLP-1 is an incretin hormone secreted by L cell in the intestine in response to food intake. GLP–1 binds to its receptor on pancreatic β–cells leading to glucose-dependent insulin secretion and thereby improvement of glycemic control.
- In addition to blood glucose reduction in Type 2 diabetes, liraglutide have been associated with **weight loss, improved β–cell function** and **a reduction in office systolic blood pressure.**[2)]
- Pronounced weight gain frequently complicates insulin therapy in pts with DM. Furthermore the fluid of Peritoneal Dialysis (PD) contains high concentrated glucose to ensure hyper-osmolarity, and glucose is absorbed. So insulin-treated pts on PD probably tend to gain weight.
- Recently the efficacy of DPP-4 inhibitors is reported in CKD patients. [3)4)]And its report is progressively increasing. However the efficacy of GLP-1 receptor agonists (RA) is uncertain. There are few reports in DM pts with CKD, in a particular CAPD or Hemodialysis (HD) pts. **In this study, we investigated the efficacy of GLP-1 RA in chronic dialysis pts (ESRD) with DM.**

Method

Study design and patient population

- This was a single-center with one satellite hospital, open-label study.
- There were 5 PD pts (3 males and 2 females, age ; 71.4 ± 6.3 years, duration of dialysis ; 4.6 ± 1.9 years) on PD: 5 HD pts (3 males and 2 females, age ; 64.4 ± 12 years, duration of dialysis ; 9.3 ± 6.0 years) on HD. We selected 10 chronic dialysis pts, who receive 2 years on PD, over 1 year on HD, of daily treatment with liraglutide (0.6 mg or 0.9 mg/day) and lixisenatide (10-20μg/day).
- We compared with the clinical parameters (physiological, chemical , etc.) basement and after 2 years or 1 year.

The specific patient eligibility criteria are listed below.

Inclusion criteria: ‣ male and female patients with type 2 diabetes and ESRD treated with a stable dose of 0.6 mg or 0.9 mg liraglutide, 10 or 20μg, lixisenatide for at least 6 months. HD:5hours/time, 3 time/week.The BP was measured at hospital coming day in PD and before HD session at the next day of 2 days free in HD pts. ‣ Patients were excluded if they had type 1 diabetes, and under 20 ys; had been treated with another incretin mimetic within 3 months prior to screening.

Statistical analysis

- Data was expressed as mean ± SD. JMP version 12.1.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.
- The Student t-test was used to assess differences in numerical variables from baseline to 1 or 2 years.
- A P value less than 0.05 was considered statistically significant.

Disccusion

- The mechanism by which GLP-1 RA reduces BP is unclear, but it might be through increased natriuresis, vasodilation from GLP-1 receptor activation, insulin subsides and suppressed the effect of angiotensin-Ⅱ [5), 8)] .
- In obese ESRD-DM pts, appetite loss due to direct thalamus stimulation by GLP-1RA leads BW (lipid) reduction, which might make BP control directly improved [9)].
- The same as some reports [6),7)] , the treatment of GLP-1 RA (liraglutide or lixisenatide) may be safe and effective not only in HD, but in PD pts.

Refference

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Result

Table1. Baseline and 2 years demographics and clinical characteristics of PD patients
GLP-1RA:mean period of use:2.5±0.2 years

	Baseline	2 years	p value
Albmin (g/dl)	2.9±0.1	3.2±0.5	0.26
Hemoglobin (g/dl)	10.8±0.8	11.7±1.0	0.14
HbA1c (%)	7.0±0.8	6.0±0.4	0.048*
Glycoalbmin (%)	19.6±3.4	15.4±1.7	0.047*
Body fat falling rate (%)*	0.0±0.0	-13.7±10.8	<0.001**
Skeletal muscle mass (kg)*	22.9±1.4	23.1±1.9	0.9
Extra-cellular water ratio*	0.399±0.01	0.403±0.01	0.18
Body weight falling rate (kg)*	0.0±0.0	-6.8±2.5	0.004**
Left ventricular mass index**	114.8±10.9	113.2±15.9	0.86
Systolic blood pressure (mmHg)	150.6±10.5	129.8±12.5	0.022*
Diastolic blood pressure (mmHg)	67.0±11.7	65.8±7.4	0.85

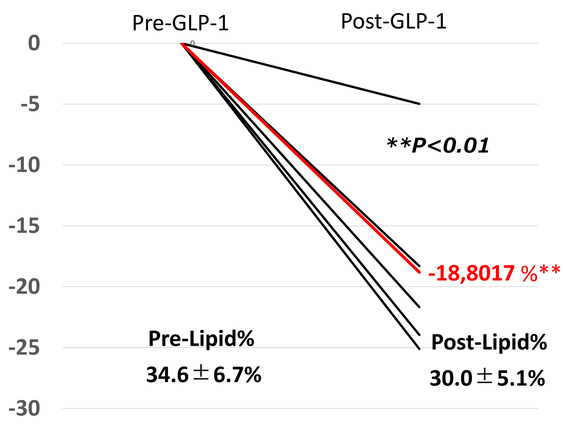
Table2. Baseline and 1 year demographics and clinical characteristics of HD patients
GLP-1RA:mean period of use:1.7±0.5 years

	Baseline	1 year	p value
Albmin (g/dl)	3.8±0.4	3.9±0.4	0.58
Hemoglobin (g/dl)	10.6±1.1	11.5±0.8	0.26
HbA1c (%)	6.6±0.6	6.1±1.0	0.4
Glycoalbmin (%)	24.4±2.8	23.1±2.9	0.5
Body fat falling rate (%)*	0.0±0.0	-33.6±32.9	0.02*
Skeletal muscle mass (kg)*	27.0±8.6	26.2±9.0	0.9
Extra-cellular water ratio*	0.403±0.01	0.400±0.01	0.6
Body weight failing rate (%)*	0.0±0.0	-6.86±5.6	0.05*
Left ventricular mass index**	126.2±31.9	115.2±21.0	0.6
Systolic blood pressure (mmHg)	158.0±9.9	141.4±7.1	0.018*
Diastolic blood pressure (mmHg)	80.2±11.8	77.6±9.8	0.7

- *Measured by Inbody 720®, bioelectrical impedance analysis
- **Measured by echocardiography

***:p<0.05**
****P<0.01**

Figure 1. Comparison of ⊿Lipid% on PD after GLP-1



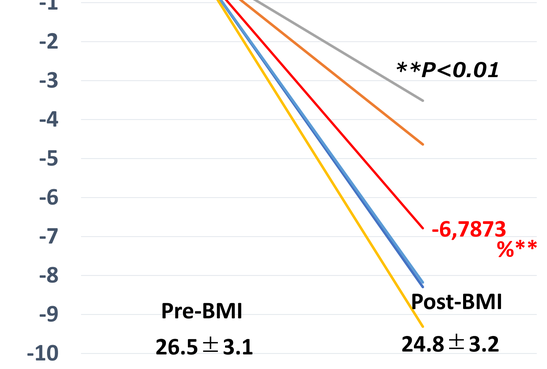


Figure 2. ⊿BW% on PD pre-and post GLP-1

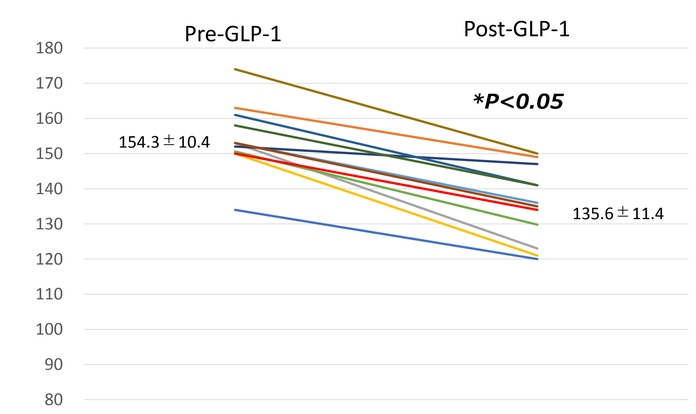


Figure 3. BP (mmHg) on ESRD-DM for pre-and post GLP-1
Arteriosclerotic marker (baPWV, ABI, CAVI); not significant between pre- and post-GLP-1

Conlusions

- SBP, BW, and body fat were significantly improved after treatment. Only in PD, HbA1c, glycoalbumin were significantly improved in PD, however not significantly in HD.
- The data of ECW/TBW, LVMI, and arteriosclerotic marker; PWV, and ABI were not significant.
- A few patients had slight anorexia, but it was very mild. None experienced hypoglycemia and other adverse events.
- We could show that the treatment of liraglutide or lixisenatide may be efficacy and safety in chronic dialysis patients.
- **The GLP-1RA therapy may be very useful to improve BP control and body fat without muscle loss in ESRD-DM.**

☞ *Our study has several limitations. There was not the control group. The study population was very small. And the reseach period was short. So we require large-scale study with longer follow-up.*

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