Favorable Effect on Blood Volume Control in Hemodialysis Patients with Type 2 Diabetes after Switching from Insulin Therapy to Liraglutide, a Human Glucagon-like Peptide-1 Analog

– Results from a Pilot Study in Japan –

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Objective: Hemodialysis patients are advised to limit the intake of foods in order to control volume status and body weight (BW). We report the clinical course of five Japanese hemodialysis patients with type 2 diabetes mellitus (T2DM) who were switched from insulin to liraglutide, and the efficacy of the treatment, especially in terms of changes in interdialysis weight gain (IDWG).
Methods: This retrospective pilot study included 5 Japanese hemodialysis patients with T2DM. Insulin and other oral hypoglycemic agents, if any, were discontinued before switching to liraglutide. The initial dose of liraglutide was set at 0.3 mg/day for more than 1 week, increased to 0.6 mg/day for more than 1 week and then, to 0.9 mg/day if needed.
Results: At baseline, the mean body mass index (BMI) was 23.2 ± 1.2 kg/m² and mean IDWG was 2.0 ± 0.4 kg. The required dose of liraglutide ranged from 0.3 to 0.9 mg/day. At the end of 3-month treatment, liraglutide reduced HbA1c level, BMI, and IDWG. A significant decrease in cardiothoracic ratio was confirmed on chest radiography.
Conclusion: Switching from insulin to liraglutide seems effective in hemodialysis patients with T2DM, especially in those with difficult blood fluid volume control associated with failure of dietary restriction.

Key words: blood volume, body mass index, glucagon-like peptide 1, hemodialysis, type 2 diabetes mellitus

INTRODUCTION

Glucagon-like peptide 1 (GLP-1), a gut hormone secreted by L-cells in the lower parts of the small intestine, is composed of 29−30 amino acids [1]. Several basic research and clinical studies have reported various physiological effects for GLP-1, including reduction of blood glucose level through glucose-dependent insulin secretion [2] and reduction of body weight (BW) induced by suppression of appetite and gastrointestinal peristalsis [3]. Previous research studies indicated the efficacy of GLP-1 in reducing elevated blood glucose levels in patients with type 2 diabetes mellitus (T2DM) [4]. However, continuous subcutaneous infusion of GLP-1 is required for clinical application because GLP-1 is rapidly degraded by di-peptidyl peptidase-4 (DPP-4) [5]. On the other hand, liraglutide, a human GLP-1 analog, is a glucose-lowering compound that can maintain the effect of GLP-1 and highly binds to albumin by adding fatty acid to human GLP-1, and can be administered once daily via subcutaneous injection [6]. Liraglutide has been included in the government-sponsored health system in Japan for clinical use since June 2010.

Most oral glucose-lowering agents are contraindicated for patients on hemodialysis because of the risk of serious hypoglycemia or adverse effects. Thus, insulin therapy is used as the basic treatment for glycemic control in such patients. However, we often experience serious hypoglycemic episodes in patients with inadequate glycemic control after the introduction of insulin therapy as a negative choice in hemodialysis patients treated with intensive insulin therapy (basal-bolus therapy) [7]. Possible reasons for the hypoglycemia in such patients include poor insulin degradation due to renal failure, leading to a residual peak in insulin concentration even when not necessary and that hemodialysis patients have poor response to the gluconeogenesis reaction during fasting and hypoglycemic state [7]. The blood glucose lowering effect of liraglutide through a glucose-dependent insulin secretion effect suggests that the use of this agent instead of insulin can potentially improve quality of life of patients and reduce their risk of hypoglycemia [8].

The interdialysis weight gain (IDWG) correlates with prognosis in patients undergoing long-term hemodialysis [9]. IDWG is considered to be controlled within 3−5% of body dry weight. It is feasible that liraglutide is superior to insulin in suppressing any increase in BW based on the abovementioned mechanism of action [3]. However, to our knowledge, only one report described switching from insulin to liraglutide therapy

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Table 1 Patient background

Patients number	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender (male/female)	Male	Male	Female	Male	Male
Age (years)	66	70	68	74	61
Height (cm)	164	160	151	170	158
Body weight (kg)	63	59.3	52	62	62
Interdialysis weight gain (kg)	1.9	1.5	1.9	2.3	2.4
Body mass index (kg/m^2)	23.4	23.3	22.8	21.5	24.8
Systolic blood pressure (mmHg)	170	131	154	184	160
Diastolic blood pressure (mmHg)	91	67	76	93	86
Hemoglobin (mg/dl)	10.1	10.9	9.6	9.5	10.5
Hematocrit (%)	30.8	33.7	29.1	29.2	30.9
Serum albumin (mg/dl)	3.9	3.9	3.5	3.0	3.9
Cardiothoracic ratio (%)	49.3	50.5	51.5	50.2	50.1
C-peptide (ng/ml)	11.3	6.4	9.8	11.4	6.1
HbA1c (%)	5.8	6.6	5.1	6.0	6.6
Total insulin dose (IU)	18	15	12	42	13

Data are mean ± SD.

in hemodialysis patients [10], and the effects of liraglutide therapy on BW, particularly changes in IDWG, have not been reported yet.

The present pilot study describes the clinical course of five Japanese hemodialysis patients with T2DM who were switched from insulin to liraglutide therapy. We analyzed the efficacy of the treatment, especially in terms of changes in blood glucose, hemoglobin A1c (HbAlc) and IDWG.

MATERIALS AND METHODS

Five patients with T2DM who underwent maintenance hemodialysis at Seichi Clinic and were switched from insulin to liraglutide therapy within 1 year, between July 2011 and July 2012, were included in this study. All patients underwent hemodialysis through an arteriovenous fistula at three days per week, with each session time lasting between 3.5 to 4 hours. The research project was approved by the Institutional Review Board for Clinical Research, Tokai University Hospital (UMIN000009638). Informed consent was obtained from each patient for inclusion in the project.

Insulin and other oral hypoglycemic agents, if any, were discontinued before switching to liraglutide. Treatment with liraglutide commenced at 0.3 mg/day for more than 1 week, and then escalated to 0.6 mg/day for more than 1 week. Finally, the dose was increased to 0.9 mg/day if needed after confirmation of tolerance. All patients tolerated the 0.6 mg/day dose, except those with strong gastrointestinal symptoms. Adjustment of the dose was at the discretion of the attending physician.

Clinical data such as pre-dialysis systolic blood pressure (SBP) and diastolic blood pressure (DBP), dry weight and IDWG, were obtained from the medical records. IDWG was calculated from the sum of the difference between the patient's weight upon entering and leaving 12 hemodialysis sessions. Body mass index (BMI) represented the average dry weight divided by the square of height in meters.

In this study, the endpoints were BW after administration of liraglutide, BMI, IDWG, changes in HbA1c level, systolic blood pressure, diastolic blood pressure, and presence of hypoglycemic episodes. Data on gender, age, BMI at initiation of liraglutide therapy, hemoglobin level, hematocrit level, serum albumin level, HbA1c level, systolic blood pressure, diastolic blood pressure, duration of T2DM, total insulin dose per day, and serum C-peptide level at initiation of hemodialysis were collected. HbA1c levels were determined by the high-performance liquid chromatography method and reported as per National Glycohemoglobin Standardization Program (NGSP) values. The results are presented as mean ± SD, and changes in parameters before and after switching to liraglutide were compared using the Wilcoxon signed-rank test. The level of significance was set at $p < 0.05$ while tendency was set at $p < 0.1$.

RESULTS

The mean age of the five patients was 67.6 ± 5.2 years, and mean HbA1c level was 6.0 ± 1.0%. All patients were switched from insulin to liraglutide therapy (Table 1). Table 2 shows details of the changes in therapeutic regimen. All patients achieved glycemic control with 0.3–0.9 mg/day of liraglutide after switching from insulin.

BW, BMI and IDWG tended to be lower at 3 months compared to before switching (baseline) (Table 3). A significant decrease in cardiothoracic ratio (CTR) was observed on chest radiography (Table 3, Figure). However, no significant changes were observed in blood pressure, hemoglobin level, hematocrit level and serum albumin level. For glycemic control, HbA1c level as well as the frequency of hypoglycemic episodes tended to decrease after switching to liraglutide. Table 4 summarizes the changes in serum albumin level, HbA1c level, BW, and IDWG over the 3-month period

Table 2 Treatment details before and after switching to liraglutide

	Before (insulin units)	3 months (mg/day)
Patient 1	A: 3-0-3-0 (HD) 3-2-7-0 (no HD) G: 0-0-0-6	Liraglutide 0.3−0.6 mg
Patient 2	A: 5-5-5-0 (HD) 0-5-5-0 (no HD)	Liraglutide 0.6 mg
Patient 3	3/7: 8-0-4-0 (HD) 7-0-4-0 (no HD)	Liraglutide 0.3−0.6 mg
Patient 4	A: 14-14-14-0	Liraglutide 0.6 mg
Patient 5	A: 3-3-3-0 (HD) 5-4-4-0 (no HD)	Liraglutide 0.9 mg

A: aspart, G: glargine, 3/7: premixed human insulin 30/70, HD: hemodialysis

Table 3 Changes in clinical parameters during treatment with liraglutide

	0 months	3 months	P value
Body weight (kg)	59.7 ± 4.5	58.6 ± 4.9	0.0625
Interdialysis weight gain (kg)	2.0 ± 0.4	1.7 ± 0.6	0.0625
Body mass index (kg/m^2)	23.2 ± 1.2	22.7 ± 1.6	0.0625
Systolic blood pressure (mmHg)	160.2 ± 19.6	158.4 ± 9.3	0.50
Diastolic blood pressure (mmHg)	82.6 ± 10.9	78.4 ± 14.0	0.50
Hemoglobin (mg/dl)	10.1 ± 0.6	9.9 ± 0.8	0.22
Hematocrit (%)	30.7 ± 1.9	29.7 ± 2.6	0.1563
Hypoglycemic episodes (time/week)	1.2 ± 0.4	0.4 ± 0.5	0.0625
Serum albumin (mg/dl)	3.6 ± 0.4	3.6 ± 0.4	0.50
Cardiothoracic ratio (%)	50.3 ± 0.8	45.8 ± 2.9	0.0313
HbA1c (%)	6.0 ± 0.6	5.7 ± 0.5	0.0625

Data are mean±SD.
NS: not significant.

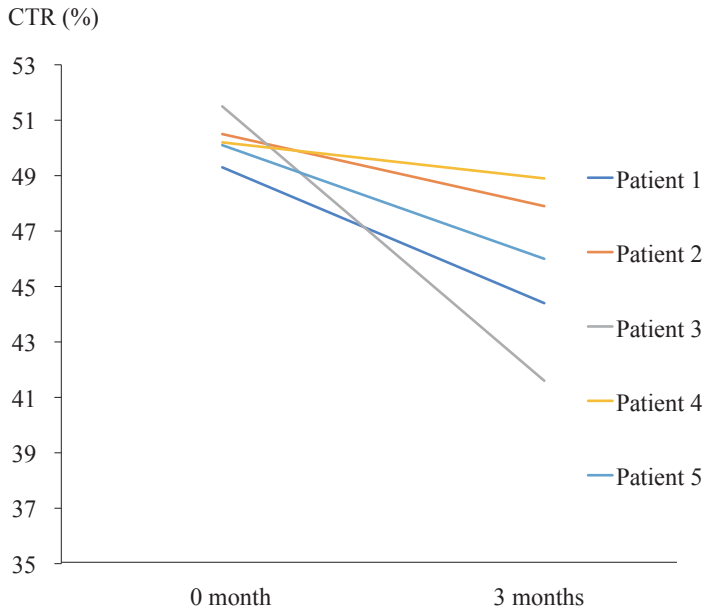

Figure Cardiothoracic ratio (CTR) change on chest radiography in each patient.

Table 4 Changes in HbA1c, dry weight and body weight during treatment with liraglutide

Liraglutide dose (mg/day)	0 month	1 month	2 months	3 months
Patient 1: 0.3–0.6 mg				
Serum albumin (mg/dl)	3.9	3.7	4.1	3.8
HbA1c (%)	5.8	6.1	5.7	5.2
DW (kg)	63.0	63.0	63.0	63.0
IDWG (kg)	1.9	1.6	2.0	1.8
Patient 2: 0.6 mg				
Serum albumin (mg/dl)	3.9	3.7	3.5	3.9
HbA1c (%)	6.6	6.4	6.1	5.8
DW (kg)	59.3	59.3	59.3	58.6
IDWG (kg)	1.5	1.0	0.6	0.9
Patient 3: 0.3–0.6 mg				
Serum albumin (mg/dl)	3.5	3.2	3.4	3.5
HbA1c (%)	5.1	5.1	4.8	5.1
DW (kg)	51.3	51.3	51.3	50.5
IDWG (kg)	1.9	1.7	1.7	1.4
Patient 4: 0.3–0.6 mg				
Serum albumin (mg/dl)	3.0	3.0	3.0	2.9
HbA1c (%)	6.0	5.9	5.9	5.9
DW (kg)	62.0	62.0	60.5	59.2
IDWG (kg)	2.3	1.8	1.8	2.3
Patient 5: 0.9 mg				
Serum albumin (mg/dl)	3.9	3.9	3.9	3.9
HbA1c (%)	6.6	6.2	6.3	6.4
DW (kg)	62.0	62.0	61.6	61.6
IDWG (kg)	2.1	2.1	2.2	2.2

A: aspart, G: glargine, 3/7: premixed human insulin 30/70, HD: hemodialysis, DW: dry weight, IDWG: interdialysis weight gain.

for all five patients.

The results of a questionnaire on quality of life administered 3 months after treatment switch, showed that more than half of the patients felt comfortable with reduced injection frequency to once a day and were aware of the reduction in the number of hypoglycemic episodes (Table 5). The results also showed that the reduction in hypoglycemic episodes led to a proactive behavior, such as going out, and high patient satisfaction.

DISCUSSION

Liraglutide, a human GLP-1 analog, is the first GLP-1 receptor agonist introduced in Japan and is characterized by enhancement of insulin secretion in a glucose-dependent manner by binding to the GLP-1 receptor of pancreatic β-cells. Thus, liraglutide lowers blood glucose level without increasing the risk of hypoglycemic episodes. This drug is also believed to prevent any increase in BW because of its suppressing effect on appetite and gastrointestinal peristalsis. Moreover, clinical data have shown a reduction in BW following liraglutide monotherapy [11]. Liraglutide is also considered suitable for diabetics on hemodialysis because no dose adjustment is required, regardless of the severity of renal impairment [12]. Liraglutide has not yet been approved in Europe because of insufficient clinical data [13], but is approved in the United States though careful administration is stipulated [14]. In this study, we investigated the feasibility of switching from insulin to liraglutide therapy in patients in whom volume control is difficult to attain because of failure of dietary restriction.

The present pilot study highlighted the following three beneficial effects for liraglutide therapy: 1) decreased HbA1c level and frequency of hypoglycemic episodes, 2) reductions in BW and IDWG, and 3) reduction in injection frequency. These effects suggest that liraglutide may contribute to improvement in quality of life and treatment compliance.

Based on improvement in HbA1c and reduction in the frequency of hypoglycemic episodes, previous studies concluded that glycemic control was improved in patients with renal failure, and that such improvement was independent of obesity, without increasing BW and that the risk of hypoglycemic episodes was lower in patients treated with liraglutide alone [15]. Our results are consistent with those of the above study. In comparison with DPP-4 inhibitors, which are widely used in hemodialysis patients, liraglutide has a stronger glucose-lowering effect [16] and maintains certain level of endogenous insulin secretion, as shown in our patients. Therefore, patients may benefit from the replacement of insulin with liraglutide therapy, given that safety is ensured in patients in whom glycemic control is achieved with relatively low doses of insulin.

We also focused on CTR and basic changes in BW and BMI. CTR is believed to be an index of body dry weight and is routinely assessed in hemodialysis patients. CTR is independently associated with left ventricular hypertrophy and cardiac dysfunction in patients with hypertension [17] and is sometimes used as a predictor of sudden death in patients with chronic heart failure [18]. In general, a large CTR is considered

Table 5 Results of questionnaire on quality of life

1. Describe the difficulty in switching insulin therapy to liraglutide	
Easier	80.0% (n = 4)
Unchanged	20.0% (n = 1)
More difficult	0
2. Has treatment with liraglutide changed the frequency of hypoglycaemic episodes compared with insulin?	
Decreased	80.0% (n = 4)
Unchanged	20.0% (n = 1)
Increased	0
3. Has treatment with liraglutide changed your activity and positivity towards life?	
More active	60.0% (n = 3)
Unchanged	40.0% (n = 2)
Less active	0
4. Has treatment with liraglutide changed your diabetes?	
Satisfied	60.0% (n = 3)
Unchanged	40.0% (n = 2)
Worse	0
5. Do you want do go back to insulin treatment?	
No, I don't	80.0% (n = 4)
No preference	20.0% (n = 1)
Yes, I do	0

a poor prognostic factor [19]. For these reasons, we investigated the effect of liraglutide on changes in CTR and BW in our hemodialysis patients. The observed changes in CTR suggest that the use of liraglutide improved body fluid volumes and body dry weight. During the observation period, no definite change in erythropoiesis stimulating agent or hematocrit level was observed. Therefore, we suggest that the appetite-suppressive effect of liraglutide appropriately adjusted dietary intake and water intake in patients with relatively large volumes of dietary intake, resulting in a significant decrease in CTR. Moreover, recent reports revealed importance of association between body composition and frailty among hemodialysis patients [20, 21]. Therefore, we also analyze the alteration of serum albumin level as an assessment of nourishment. There is no significant alteration of serum albumin level during the observation period. However, from the view point of safety and avoiding frailty, further studies including long and large study are needed.

Attention to the following two points, especially in hemodialysis patients, is important for administration of GLP-1 receptor agonists for suppressing dietary intake: 1) optimal liraglutide dose and adverse effects, including gastrointestinal symptoms, and 2) reduction in the appetite-suppressive effect after long-term use.

Although various clinical conditions of patients and indications for use of GLP-1 receptor agonists and safety concerns in hemodialysis patients have been reported, there are no standardized indications for use of liraglutide. Although liraglutide is not contraindicated, high prevalence rates of diabetic autonomic neuropathy and diabetic gastrointestinal paresis as comorbidities were reported in hemodialysis patients with diabetes [22]. In fact, other studies reported that the compliance of hemodialysis patients to liraglutide therapy remained at 50% because of unfavorable symptoms, including nausea and vomiting [10]. In T2DM patients with normal renal function, the dose of liraglutide is usually increased from 0.3 to 0.9 mg at intervals of 1 week or longer. In this study, we instructed most patients in advance to adjust the dose (preferably to 0.6 mg/day) by themselves. We believe this approach was directly responsible for the high compliance rate observed in our patients. Only one of the five patients received the maximum dose (0.9 mg), while the rest of the patients received 0.6 mg of liraglutide or less. This suggests that while the appetite-suppressive effect was enhanced along with an increase in the dose to up to 0.9 mg/day, attention should be paid to the risk of treatment discontinuation because of gastrointestinal symptoms.

Most patients in this study achieved glycemic control without increasing the dose to 0.9 mg/day. One possible reason for this is that these patients maintained endogenous insulin secretion at a certain level. Liraglutide is potentially clinically useful for hemodialysis patients, especially those in whom volume control is difficult to attain because of failure of dietary restriction. It should be noted, however, that GLP-1 receptor agonists are contraindicated in insulin-dependent patients with T2DM or T1DM because of reduced insulin secretion. Serum C-peptide levels measured in casual blood samples showed that the five patients included in this study were not insulin-dependent. Therefore, confirmation of endogenous insulin secretion status is critically important in terms of safety when switching insulin to liraglutide in hemodialysis patients.

Liraglutide was reported to have less adverse gastrointestinal effects, such as vomiting, than lixisenatide, since liraglutide is a long-acting GLP-1 receptor agonist [23]. While the safety profile of liraglutide is favorable, the onset of tachyphylaxis in patients treated with GLP-1 receptor agonists has recently raised concerns in terms of the persistent appetite-suppressive effect [24]. Thus, more data regarding the effects of liraglutide on BW attenuation and appetite-suppression should be accumulated.

The present study has certain limitations. First, the

study included a small sample size of five patients. Data validation in a larger population sample is necessary. Second, the favorable effect on BW diminished within 3 months in some patients, warranting long-term statistical analysis in a larger sample size, including the above-mentioned contributing effect on the persistent tachyphylactic effect. Third, the study did not examine the effect of liraglutide after switching from oral glucose-lowering agents. Further studies are needed to examine whether liraglutide is more efficacious than these drugs.

Although this study was conducted at a single institution and in a small sample population, it is the first to provide detailed description of changes in blood glucose level and BW in hemodialysis patients with T2DM who were switched from insulin to liraglutide therapy. In the future, case-series multi-center cohort or intervention studies are needed to establish the true effects of liraglutide in T2DM hemodialysis patients.

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STATEMENT OF CONFLICT

The authors declare no conflict of interest in relation to this article.

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