Possibility of switching from liraglutide to oral hypoglycemic agents as a useful therapeutic option for obese Japanese type 2 diabetics

Masanori Iwanishi*, Choka Azuma, Yuji Tezuka, Yukako Yamamoto, Jun Ito-Kobayashi & Miki Washiyama

ABSTRACT

Objective: Our aim was to examine the influence of switching to oral hypoglycemic agents on post-switching weight loss and blood glucose control in obese Japanese patients with type 2 diabetes after long-term therapy with a glucagon-like peptide 1 (GLP-1) receptor agonist. Methods: In 8 obese patients with type 2 diabetes, oral hypoglycemic agents were introduced after long-term therapy with a GLP-1 receptor agonist, liraglutide, based on their wishes. We investigated the oral glucose tolerance test (OGTT) and the subsequent changes in HbA1c and body weight in all patients. Results: Concerning the patient background, the mean age was 44.4 years. The mean body mass index (BMI) was 30.0 kg/m^2, and the mean duration of diabetes was 0.3 years. The mean HbA1c value before liraglutide administration was 10.3%. The mean liraglutide treatment period was 1.1 years. The mean HbA1c value on switching liraglutide to oral hypoglycemic agents was 5.7%. The mean rate of change in the body weight after liraglutide administration was -9.2 kg, and the mean BMI upon switching liraglutide to oral hypoglycemic agents was 26.8 kg/m^2. The oral hypoglycemic agents consisted of DPP-4 inhibitors in 7 patients, SGLT2 inhibitors in 3, and metformin in 1. In 4 of the 8 patients, weight gain was noted. The OGTT demonstrated that insulin secretion was maintained in the subjects. Conclusion: Our observation suggested the possibility that the therapeutic strategy of administering liraglutide and switching to oral hypoglycemic agents after confirming maintenance of weight loss and normal HbA1c value for a specific period might be useful for treating type 2 diabetics with a relatively short duration of diabetes during the initial phase after diagnosis, This therapy may become a new treatment option, although our report included small patient numbers and this strategy warrant the need for further investigation.

Introduction

When treating Japanese patients with type 2 diabetes, diet/exercise therapies are generally performed. For obese patients, metformin is prescribed as a first-choice drug, and oral hypoglycemic agents, such as dipeptidyl peptidase-4 (DPP-4) and sodium-glucose cotransporter 2 (SGLT2) inhibitors, which may not induce hypoglycemia, are additionally administered when blood glucose control is unfavorable. When it remains unfavorable despite this therapy, administration of sulfonylurea (SU) agents, glucagon-like peptide -1 (GLP-1) receptor agonists, or insulin is considered. On the other hand, for non-obese patients, DPP-4 inhibitors are prescribed as first-choice drugs, and administration of SU agents, GLP-1 receptor agonists, or insulin is considered when blood glucose control is unfavorable. Thus, in Japan, the prescription of GLP-1 receptor agonists is considered in many cases when blood glucose control is unfavorable after the administration of 2 or 3 oral hypoglycemic agents. Furthermore,

Department of Diabetes and Endocrinology,Kusatsu General Hospital 1660 Yabase,Kusatsu Shiga 525-8585 , Japan

**Author for correspondence: masa-iwani@solid.ocn.ne.jp*

KEYWORDS

- a glucagon-like peptide -1 receptor agonist
- liraglutide
- oral hypoglycemic agents
- obese Japanese type 2 diabetics

there are often cases in which the GLP-1 receptor agonist administration period was relatively short because the drug was promptly switched to an oral hypoglycemic agent after blood glucose improvement despite the early introduction of a GLP-1 receptor agonist. According to the American Diabetes Association (ADA), GLP-1 receptor agonists may be selected after metformin administration [1]. According to the algorithm for the treatment of type 2 diabetes prepared by the American Association of Clinical Endocrinologists (AACE), GLP-1 receptor agonists are available as first-choice drugs [2]. A recent study proposed that GLP-1 receptor agonists should be selected as first-choice drugs when deciding drug therapy for obese patients with type 2 diabetes [3]. However, no study has reported the efficacy of a therapeutic strategy in which a GLP-1 receptor agonist is initially administered to type 2 diabetics with a relatively short duration of diabetes during the initial phase after diagnosis, and then switched to an oral hypoglycemic agent after confirming maintenance of weight loss and normal HbA1c value for a specific period; this strategy is not routine. We initially administered the GLP-1 receptor agonist liraglutide to 8 obese type 2 diabetics with a relatively short duration of diabetes during the initial phase after diagnosis for a relatively long period (mean administration period: 1.2 years, range: 0.3 to 2.9 years), and switched it to oral hypoglycemic agents based on their wishes to examine the subsequent changes in the blood glucose level and body weight.

Results

■ Case 1

The patient was a 50-year-old male. A health checkup indicated that his HbA1c value was 10.0%, and he was referred to our department. The height, body weight, and BMI were 168 cm, 97 kg, and 34.4 kg/m^2, respectively. The patient was admitted for education for 2 weeks. Treatment was started with a diabetic diet at 1,200 kcal, 2 units of Novorapid (immediately before each meal), 2 units of Lantus (evening), and a total of 8 units of insulin. After 7 days, blood glucose control was improved, and 0.3 mg of liraglutide was subcutaneously injected for 4 days. Subsequently, the dose was switched to 0.6 mg. After 4-month administration, the HbA1c value was 5.4%; blood glucose control was improved. The body weight was 77 kg, demonstrating an approximately 20-kg decrease. Subsequently, sitagliptin (50 mg/day) was administered, and the HbA1c was normalized for 1 year and 4 months. There was a further 2-kg decrease in body weight. After discharge, a diabetic diet at approximately 1,800 kcal was introduced based on the patient's wishes. Concerning exercise, training with a bicycle ergometer was performed for 20 minutes (corresponding to approximately 4 Metz of exercise) 3 times a day during admission, with a maximum heart rate of 40%, which was established in accordance with age. After discharge, the patient walked for 1 hour every day.

■ Case 2

The patient was a 25-year-old male. On measurement using his mother's self-glucose-measuring instrument, the blood glucose level was 300 mg/dL, and he consulted our department due to the risk of diabetes mellitus. His height, body weight, and BMI were 170.1 cm, 104 kg, and 36.0 kg/m^2, respectively. His HbA1c value was 11.3%. The patient was admitted for education for 2 weeks. Treatment was started with 4 units of Novorapid (immediately before each meal), 4 units of Lantus (evening), and a total of 16 units of insulin. After 6 days, blood glucose control was improved, and the regimen was switched to liraglutide. After 0.3 mg of liraglutide was administered for 4 days, the dose was switched to 0.6 mg. The liraglutide administration period was 1 year and 5 months. The HbA1c value was normalized 3 months after the start of administration. The normalization was also maintained after switching to alogliptin (12.5mg/day). After the start of liraglutide administration, there was a 16-kg decrease in body weight. His HbA1c value has been normalized for over 3 years and 7 months after switching to alogliptin, but there was an approximately 4-kg rebound in body weight. During liraglutide administration, a diabetic diet at 1,200 kcal was given, and the calorie intake was increased to 1,600 to 1,800 kcal after switching to alogliptin. During admission, training with a bicycle ergometer was performed for 20 minutes (corresponding to approximately 4 Metz of exercise), with a maximum heart rate of 60%, which was established in accordance with age. After discharge, no specific exercise program was arranged.

■ Case 3

The patient was a 44-year-old male. His height, body weight, and BMI were 171.0 cm, 83.0 kg, and 28.4 kg/m^2, respectively. Although sitaglipitin

(50 mg) was administered by family doctor, his HbA1c value was 9.4%. He was introduced to our department, sitaglipitin was stopped and 0.9 mg of liraglutide and metformin (500 mg) was administered for 1 year and 2 months. The HbA1c value was normalized 3 months after the start of administration. The normalization was also maintained after switching to sitagliptin (50 mg/day) and ipragliflozin (50 mg/day). After the start of liraglutide administration, there was a 8 kg decrease in body weight. His HbA1c value has been normalized for 6 months after switching to sitagliptin and ipragliflozin, and there was a 7 kg decrease in body weight. During liraglutide administration, a diabetic diet at 1,600 kcal was given.

■ Case 4

The patient was a 50-year-old male. His height, body weight, and BMI were 174.0 cm, 80.0 kg, and 26.4 kg/m2, respectively. When he was admitted to our hospital for treatment of abscess, an HbA1c of 9.4% value was pointed out. 0.6 mg of liraglutide after insulin treatment for two weeks was administered for 7 months. The HbA1c value was normalized 3 months after the start of administration. The favorable HbA1c level was also maintained after switching to linagliptin (5 mg). After the start of liraglutide administration, there was a 8-kg decrease in body weight. His favorable HbA1c value has been maintained for one year and 6 months after switching to linagliptin, but there was a 4 kg rebound in body weight. During liraglutide administration, a diabetic diet at 1,600 kcal was given.

■ Case 5

The patient was a 53-year-old female. Her height, body weight, and BMI were 157.0 cm, 72.0 kg, and 29.2 kg/m^2, respectively. She was introduced to our department for glycemic control to receive cataract operation. An HbA1c of 12.8% value was pointed out. 0.6 mg of liraglutide and metformin (500 mg/day) was administered for 7 months. The HbA1c value was normalized 5 months after the start of administration. The favorable HbA1c level was also maintained after switching to sitagliptin (50 mg/day) and metformin (1000 mg/day). After the start of liraglutide administration, there was a 11 kg decrease in body weight. Her favorable HbA1c value has been maintained for 11 months after switching to sitagliptin and metformin, but there was a 4.6 kg rebound in body weight. During liraglutide administration, a diabetic diet at 1200 kcal was given.

■ Case 6

The patient was a 60-year-old male. His height, body weight, and BMI were 167.5 cm, 82.6 kg, and 29.6 kg/m^2, respectively. As an HbA1c of 10.2% value was pointed out by his family doctor. He was introduced to our department for glycemic control. The patient was admitted for education for 2 weeks. 0.3 mg of liraglutide after insulin treatment for 10 days was administered for 2.1 years. The HbA1c value was normalized 2 months after the start of administration. The HbA1c was also maintained after switching to sitagliptin (50 mg/day). After the start of liraglutide administration, there was a 10.4 kg decrease in body weight. His normalized HbA1c value has been maintained for 2.3 years after switching to sitaglipitin, but there was a 1.1 kg rebound in body weight. During liraglutide administration, a diabetic diet at 1,200 kcal was given.

■ Case 7

The patient was a 39-year-old male. His height, body weight, and BMI were 173.0 cm, 94.0kg, and 31.4 kg/m^2, respectively. As an HbA1c of 7.7% value was pointed out by his family doctor. he was introduced to our department for glycemic control. The patient was admitted for diabetic education for 2 weeks. 0.6 mg of liraglutide was administered for 8 month. The HbA1c value was normalized 2 months after the start of administration. The HbA1c was also maintained after switching to sitagliptin (50 mg/day). Empagliflozin (10 mg/day) was added to him for reduction of body weight during clinical course. After the start of liraglutide administration, there was a 10.4kg decrease in body weight. His normalized HbA1c value has been maintained for 2.0 years after switching to sitaglipitin and empagliflozin, but there was a 5.2 kg rebound in body weight. During admission, a diabetic diet at 1,200 kcal was given.

■ Case 8

The patient was a 34-year-old male. His height, body weight, and BMI were 168.0 cm, 70.5 kg, and 25.0 kg/m^2, respectively. An HbA1c of 7.7% value was pointed out, when he had a consultation with ophthalmologist for the evaluation of cataract. The patient was admitted for diabetic education for 3 weeks. 0.6 mg of liraglutide was administered for 2.9 years. The HbA1c value was normalized 2 months after the start of administration. The HbA1c was also maintained

after switching to dapagliflozin (50 mg/day). After the start of liraglutide administration, there was a 12.0 kg increase in body weight. His normalized HbA1c value has been maintained for 1.9 years after switching to dapagliflozine, but there was a 14.1 kg decrease in body weight. During liraglutide administration, a diabetic diet at 1,200 kcal was given. We experienced 8 obese patients with type 2 diabetes, oral hypoglycemic agents were introduced, based on their wishes after long-term therapy with a GLP-1 receptor agonist, liraglutide. The background of the 8 type 2 diabetics is shown as in **TABLES 1 AND 2**. The mean age was 44.4 years. The subjects consisted of 7 males and 1 female. The mean BMI was 30.0 kg/m^2, and the mean duration of diabetes was 0.3 years. The mean estimated glomerular filtration rate (eGFR) was 98.1 mL/min/1.73 m^2 (data not shown), and the mean CPR index in 7 patients was 2.0. The mean HbA1c value before liraglutide administration was 10.3%. Concerning treatment before liraglutide administration, no treatment was performed for 2 patients, DPP-4 inhibitors were administered to 2, and insulin was administered to 4. With respect to complications, retinopathy was absent in 8 patients, and nephropathy was absent in 7. Microalbuminuria was noted in 1. There was no neuropathy in any patient. The clinical course of 8 patients in whom liraglutide was switched to oral hypoglycemic agents is shown in **(TABLE 1)**. Its summary is presented as follows. There were 8 obese (BMI: ≥ 25) patients. Five patients had a BMI of 25 to 29, and 3 had a BMI of ≥ 30. In the obese patients, the doses of liraglutide were 0.9 mg in 1 patients and 0.6 mg in 7 patients. The mean treatment period was 1.1 years. The mean HbA1c value upon switching liraglutide to oral hypoglycemic agents was 5.7%.The oral hypoglycemic agents consisted of DPP-4 inhibitors in 7 patients, SGLT2 inhibitors in 3, and metformin in 1. The mean HbA1c value at the final consultation was 5.8%, with a mean follow-up of 2.2 years after switching. The mean rate of change in body weight after liraglutide administration was -9.2 kg, and the mean BMI upon switching liraglutide to oral hypoglycemic agents was 26.8 kg/m^2. In 2 patients, the BMI decreased to <25 (pretreatment BMI: 25 to 29). The mean rate of change in body weight after switching was -1.0 kg. In 4 of the 8 patients, weight gain was noted. The results of OGTT, BMI at OGTT, CPR index after fasting, and each parameter of insulin secretion/resistance obtained from OGTT for the 8 patients are presented in **TABLE 2**. In all patients, an oral glucose tolerance test (OGTT) was conducted to evaluate insulin secretion/tolerance after weight reduction and HbA1c normalization during liraglutide treatment. The mean CPR index was 2.0, and the mean HOMA-β was 84.0. The mean insulinogenic index was 0.5. The mean HOMA-R was 1.4. The mean Matsuda Index was 7.4, and the mean disposition index was 1.5.

Discussion

We found that post-switching blood glucose control was favorable in 8 obese type 2 diabetic patients with a relative short duration of diabetes during the initial phase after diagnosis, in whom oral hypoglycemic agents were introduced, based on their wishes after long-term therapy with liraglutide, and that the body weight was relatively favorably maintained despite an increase in the rebound rate. Three factors associated with this are described below. First, weight loss was an important factor. The GLP-1 receptor agonist liraglutide exerts body-weight-reducing effects through the suppression of gastrointestinal peristalsis and feeding central function in hypothalamus and is emphasized as an important drug for type 2 diabetes with obesity [3]. Weight loss might have contributed to the improvement in glycaemic control, improving insulin sensitivity. As liraglutide treatment reduced emotional eating behavior, sense of hunger and requirement for fat [4], it is conceivable that these changes in eating behavior may influence on the maintenance of body weight after switching to oral hypoglycemic agents from liraglutide. In 566 patients with diabetes at the diabetes outpatient clinic of our hospital and 21449 patients with diabetes in 2012 Shiga Diabetes Clinical Survey [5], patients with a BMI of 25 to 29 account for approximately 75% of obese diabetics. Of 8 subjects, 5 had a BMI of 25 to 29, and 3 had a BMI of ≥ 30. The mean rate of change in body weight was -9.2 kg, and the mean BMI before and after the start of administration was 30.0 and 26.8, respectively, demonstrating a decrease. In 1 patients, the BMI decreased to <25 (pretreatment BMI: 25 to 29). With liraglutide-administration-related weight loss (approximately 10 kg), the rate of patients with a BMI of approximately 25 increased, especially among those with a pretreatment BMI of 25 to 29. Thus, almost patients in this report had sufficient reduction of body weight. This may be caused by early administration of liraglutide during the initial phase after diagnosis. Insulin

Table 1. Clinical course after switching from liraglutide to oral hypoglycemic agents

Patient	Age (y)	M/F	Height (cm)	BW (kg)	BMI (kg/m^2)	Duration of Diabetes (y)	Medication before LiraT	HbA1c before LiraT (%)	Dose of Lira (mg)	OHA during LiraT	Duration of LiraT (y)	Time to HbA1c Normalization (month)	HbA1c at switching to OHA (%)	OHA	Observational period after switching to OHA (y)	HbA1c at Final visit (%)	Change of BW (kg) After LiraT	BMI (kg/m^2) after LiraT	Change of BW after switching to OHA (kg)
1	50	M	168.0	97.0	34.4	0	Ins	10.0	0.6	(-)	0.3	1	5.4	S50 mg	2.1	5.5	-20.0	27.3	-1.0
2	25	M	170.1	104.0	35.9	0	Ins	11.3	0.6	(-)	0.3	3	5.6	A12.5 mg	6.0	5.7	-14.0	31.1	-0.7
3	44	M	171.0	83.0	28.4	2	S50 mg	9.4	0.9	ME500 mg	1.2	3	6.0	S50 mg I50 mg	0.5	5.8	-8.0	25.6	-7.0
4	50	M	174.0	80.0	26.4	0	Ins	9.2	0.6	(-)	0.6	3	5.8	L5 mg	1.5	6.3	-8.0	23.8	4.0
5	53	F	157.0	72.0	29.2	0	(-)	12.8	0.6	ME500 mg	0.6	5	6.1	S50 mg ME1000 mg	0.9	6.3	-11.0	24.7	4.6
6	60	M	167.5	82.6	29.4	0.08	Ins	10.2	0.6	(-)	2.1	2	5.6	S50 mg	2.3	6.1	-10.4	25.7	1.1
7	39	M	173.0	94.0	31.4	0.08	L5 mg	7.7	0.6	(-)	0.7	4	5.2	S50 mg E10 mg	2.0	5.7	-14.0	26.5	5.2
8	34	M	168.0	70.5	25.0	0	(-)	11.7	0.6	(-)	2.9	2	5.6	D50 mg	1.9	5.2	12.0	29.3	-14.1
Patient (n=8)	44.4 (11.3)	7/1	168.6 (5.3)	85.4 (11.8)	30.0 (3.7)	0.3 (0.7)		10.3 (1.6)			1.1 (0.9)	2.9 (1.2)	5.7 (0.3)		2.2 (1.7)	5.8 (0.4)	-9.2 (9.4)	26.8 (2.4)	-1.0 (6.6)

The means ±SD in Patient are in the bottom. The figures in parentheses are SD. M: Male F: Female y: Year Ins:Insulin A: Alogliptin S: Sitagliptin L: Linagliptin I: Ipragliflozin D: Dapagliflozin E: Empagliflozin ME: Metformin Lira: Liraglutide LiraT: Liraglutide treatment OHA: oral hypoglycemic agent BW: Body weight

Table 2. Oral glucose tolerance test and profile of insulin secretion and insulin resistance in patients with type 2 diabetes														
Patient	BMI (kg/m^2) at OGTT		Time min)				HOMA-R	HOMA-β	Matsuda Index	Disposition Index	Insulinogenic Index	FBS (mg/dl)	F-CPR (ng/dl)	CPR index
			0	30	60	120								
1	25.2	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	84 3.0	102 20.4	97 32.2	67 6.1	0.6	51.4	15.3	3.3	1.0	125	2.5	2.0
2	34.9	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	95 6.6	149 16.1	202 33.1	191 39.6	1.5	74.3	5.8	0.9	0.2	101	1.8	1.8
3	25.3	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	94 7.9	168 31.1	207 97.6	84 63.1	1.8	91.7	3.8	1.5	0.3	ND	ND	ND
4	23.0	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	102 4.9	162 14.1	212 31.0	122 32.3	1.2	45.2	7.2	1.0	0.2	110	2.0	1.8
5	26.0	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	125 5.2	195 12.4	274 21.9	285 23.4	1.6	30.2	6.0	0.4	0.1	133	2.6	2.0
6	27.1	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	87 4.8	160 7.0	203 26.6	137 24.8	1.0	72.0	9.0	1.0	0.03	102	1.2	1.2
7	29.7	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	76 8.3	139 58.1	154 99.9	92 37.4	1.6	230.0	4.5	2.3	0.8	82	3.2	3.9
8	21.9	Plasma glucose (mg/dL) Plasma insulin (μU/mL)	95 6.8	96 8.0	101 14.2	178 55.8	1.6	77.0	7.7	1.4	1.2	110	1.4	1.3
Mean (SD)	26.6 (4.1)						1.4 (0.4)	84.0 (62.2)	7.4 (3.6)	1.5 (0.9)	0.5 (0.5)	109.0 (16.7)	2.1 (0.7)	2.0 (0.9)

The means ±SD in Patient are in the bottom. The figures in parentheses are SD. OGTT: Oral Glucose Tolerance Test

secretion capacity is preserved in the patients with type 2 diabetes during the initial phase after diagnosis. As Takabe et al. reported that liraglutide causes to improve early insulin secretion [6], it is conceivable that decreased total amounts of insulin, caused by improvement of early insulin secretion may lead to reduction of body weight. The mean HOMA-R was 1.4, suggested mild insulin resistance. This may be due to weight reduction. DPP-4 inhibitors were reported to be more effective in non-obese type 2 diabetics than in obese type 2 diabetics [7,8]. DPP-4 inhibitors were used in 7 patients among oral hypoglycemic agents. As a factor involved in favorable post-switching blood glucose control, weight loss may have increased the efficacy of DPP-4 inhibitors. Second, the use of a self-glucose-measuring instrument facilitated blood glucose checking before and after meals, enhancing education. In the health insurance system of Japan, self-glucose-measuring instruments are lent to patients using liraglutide from hospitals. Blood glucose measurement before and after meals improves the understanding of the target blood glucose level and HbA1c value. Self-assessment of the effects of diet/exercise therapies through blood glucose measurement is also advantageous for favorable blood glucose control. Third, there were 7 patients with a relatively short duration of diabetes (<1 year), and insulin secretion was preserved to some degree. The mean CPR index (2.0) and disposition index (1.5) from the OGTT suggested the preservation of insulin secretion in 8 subjects. It was reported that the efficacy of liraglutide and DPP-4 inhibitors in insulin-secretion-preserved patients was more potent than in insulin-secretion-affected patients [6,9,10]. Therefore, initial therapy with liraglutide may cause potent hypoglycemic effects in insulin-secretion-preserved patients with a short interval from the diagnosis of type 2 diabetes, leading to the complete normalization of HbA1c.Treating early and effectively with combination of oral hypoglycemic agents was recommended for the management of type 2 diabetes, but has the problem that patients are reluctant to move to polypharmacy [11]. Recently, clinical inertia was reassessed, raising a clinical issue: drug therapy cannot be intensified when blood glucose control in patients with type 2 diabetes is unfavorable [12]. It was reported that 5-year blood glucose control in patients with type 2 diabetes in whom treatment was intensified within 6 months after the start of treatment was more favorable than in those in whom intensified treatment was delayed [13]. Complete HbA1c normalization may be advantageous for future diabetes care. Furthermore, in this report, the rate of patients with a short duration of diabetes was high, and we targeted the complete normalization of HbA1c. The average time to normalization of HbA1c was 2.9 months. The maintenance of complete normalization of blood glucose control in the initial phase of diabetes may lead to preserve β cell function [14] and result in the lowest risk of complications and legacy effects, as indicated in the UKPDS [15], which may be therapeutically advantageous. However, as early worsening of diabetic retinopathy was reported to be associated with the rapidity and magnitude of improvement in glycemic control with insulin and semaglutide [16], we have to keep this phenomenon in mind, especially in patients with pre-existing diabetic retinopathy when we prescribe GLP-1 receptor agonists. The early introduction of liraglutide in type 2 diabetics may be a method to overcome clinical inertia and resistance to move to polypharmacy. Even if blood glucose control becomes unfavorable after switching to oral hypoglycemic agents or there is a marked rebound in body weight, the additional introduction of liraglutide may be readily accepted by patients. As liraglutide is more potent in hypoglycemic effect than SU agents and DPP-4 inhibitors [17,18], a smaller variety of drugs to intensify blood glucose control may be required. This report does not mean that initially administering liraglutide and switching to oral hypoglycemic agents is effective in all patients with type 2 diabetes. If we switch to oral hypoglycemic agent in patients who did not show reduction of body weight or who did not have HbA1c normalization or who had severe insulin deficiency, the result may be different from our result. Although almost patients had sufficient reduction of body weight in this report, we did not intentionally select the subjects, who had sufficient reduction of body weight. This report also does not mean we demonstrate the effectiveness of this strategy. Our report included small subjects and we need a randomized prospective clinical trial with more cases to demonstrate the effectiveness of our strategy. However, our observation suggested the possibility that this strategy may lead to maintain favorable blood glucose level and body weight. In conclusion, in this report, we suggested the possibility of the strategy of initially administering liraglutide and switching to oral hypoglycemic agents after confirming weight

loss and HbA1c normalization for a specific period in type 2 diabetics with a relatively short duration of diabetes during the initial phase after diagnosis as a useful therapeutic option for Japanese patients with type 2 diabetes, although our report included small patients numbers and warrant the need for further investigation.

References

1. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2018 *Diabetes. Care.* 41(Suppl1), S73–S85 (2018).
2. Garber A, Abrahamson M, Barzilay J, *et al.* Consensus statement by the american association of clinical endocrinologists and american college of endocrinology on the comprehensive type 2 diabetesmanagement algorithm-2018 executive summary. *Endcr. Prac.* 24(1), 91–120 (2018).
3. Abdul-Ghani M, DeFronzo R. Is ıt time to change the type 2 diabetes treatment paradigm? Yes! GLP-1RAs should replace metformin in the type 2 diabetes algorithm. Diabetes. Care. 40(8), 1121–1132 (2017).
4. Fujishima Y, Maeda N, Inoue K, *et al.* Efficacy of liraglutide, a glucagon-like peptide-1(GLP-1) analogue, on body weight, eating behavior, and glycemic control, in Japanese obese type 2 diabetes. *Cardiovasc. Diabetol*. 14, 107 (2012).
5. Miyazawa I, Kadota A, Miura K, *et al*. Twelve-year trends of increasing overweight and obesity in patients with diabetes: The shiga diabetes clinical survey. *Endocr. J.* 65(5), 527–536 (2018).
6. Takabe M, Matsuda T, Hirota Y, *et al.* C-peptide response to glucagon challenge is correlated with improvement of early insulin secretion by liraglutide treatment. *Diabetes. Res. Clin. Pract.* 98(3), e32–35 (2012).
7. Maeda H, Kubota A, Kanamori A, *et al.* Long-term efficacy and safety of sitagliptin in the treatment of Japanese Type 2 diabetes (ASSET-K1) to a target of HbA1c<7%. *J. Endocrinol. Invest.* 36(8), 568–573 (2013).
8. Kim Y, Hahn S, Oh T, *et al.* Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: A systematic review and meta-analysis. *Diabetolgia*. 56(4), 696–708 (2013).
9. Kubota A, Yabe D, Kanamori A, *et al.* Factors influencing the durability of the glucose-lowering effect of sitagliptin combined with a sulfonylurea. *J. Diabetes. Investig*. 5(4), 445–448 (2014).
10. Usui R, Yabe Y, Kuwata H, *et al.* Retrospective analysis and efficacy of liraglutide monotheraphy and sulfonylurea-combination theraphy in Japanese type 2 diabetes: Association of remaining β-cell function and achievement of HbA1c target one year after initiation. *J. Diabetes. Complications*. 29, 1203–1210 (2015).
11. Pantalone K, Wells B, Chagin K, *et al.* Intesification of diabetes therapy and until A1C goal attainment among patients with newly diagnosed type 2 diabetes who fail metformin monotheraphy with a large ıntegrated healthy system. *Diabetes. Care*. 39(9), 1527–1534 (2016).
12. Khunti K, Andersen M, Wolden M, *et al.* Clinical ınertia in people with type 2 diabetes. *Diabetes. Care*. 36(11), 3411–3417 (2013).
13. Del Prato S, Felton A, Munro N, *et al.* Improving glucose management: Ten steps to get more patients with type 2 diabetes to glycaemic goal. *Int. J. Clin. Pract*. 59(11), 1345–1355 (2005).
14. Harrison LB, Adams-Huet B, Raskin P, *et al.* β-cell function preservation after 3.5 years of ıntensive diabetes therapy. *Diabetes. Care*. 35,1406–1412 (2012).
15. Holman R, Paul S, Angelyn Bethel, *et al.* 10-year follow-up of ıntensive glucose control in type 2 diabetes. *N. Engl. J. Med.* 359,1577–1589 (2008).
16. Vilsboll T, Bain S, Leiter L, *et al.* Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes. Obes. Metab*. 20(4), 889–897 (2018)
17. Seino Y, Rasmussen M, Nishida T, *et al.* Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. *Curr. Med. Res. Opin.* 26(5), 1013–1022 (2010).
18. Pratley R, Nauck M, Bailey T, *et al.* 1860-LIRA-DPP-4 study group liraglutide versus sitagliptin for patients with type 2 diabetes did not have adequate glycaemic control with metformin: A 26-week, randomized, parallel-group, open-label trial. *Lancet.* 375(9724), 1447–1456 (2010).