ORIGINAL ARTICLE

Liraglutide is effective in type 2 diabetic patients with sustained endogenous insulin-secreting capacity

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ABSTRACT

Aims/Introduction: Recently, glucagon-like peptide-1 (GLP-1) receptor agonists of liraglutide have become available in Japan. It has not yet been clarified what clinical parameters could discriminate liraglutide-effective patients from liraglutide-ineffective patients.
Materials and Methods: We reviewed 23 consecutive patients with type 2 diabetes admitted to Osaka University Hospital for glycemic control. All of the patients were treated with diet plus insulin (or plus oral antidiabetic drugs) to improve fasting plasma glucose (FPG) and postprandial glucose below 150 and 200 mg/dL, respectively. After insulin secretion and insulin resistance were evaluated, insulin was replaced by liraglutide. The efficacy of liraglutide was determined according to whether glycemic control was maintained at the target levels.
Results: Liraglutide was effective in 13 of 23 patients. There were significant differences in the parameters of insulin secretion, including fasting C-peptide (F-CPR), C-peptide index (CPI), insulinogenic index (I.I.) and urine C-peptide (U-CPR), between liraglutide-effective and -ineffective patients. The duration of diabetes was significantly shorter in liraglutide-effective patients than in liraglutide-ineffective patients. In receiver operating characteristic analyses, the cut-off value for predicting the efficacy of liraglutide was 0.14 for I.I., 1.1 for CPI, 1.5 ng/mL for F-CPR, 33.3 µg/day for U-CPR and 19.5 years for duration of type 2 diabetes.
Conclusions: Insulin secretion evaluated by F-CPR, CPI, I.I., U-CPR and the duration of type 2 diabetes were useful parameters for predicting the efficacy of liraglutide in patients with type 2 diabetes. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00168.x, 2012)

KEY WORDS: Glucagon-like peptide-1, Incretin, Type 2 diabetes

INTRODUCTION

The prevalence of type 2 diabetes has been increasing rapidly in the world[1]. According to the National Health and Nutrition Survey in Japan, the number of possible cases with diabetes has also been increasing in Japan: the prevalence was estimated at 13.7 million in 1997, 16.2 million in 2002, 18.7 million in 2006 and 22.1 million in 2007[2]. This is also the case in other Asian countries[1,3]. It is necessary to develop effective and efficient therapeutic strategies for type 2 diabetes. Recently, incretin-related drugs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have become available in Japan. In Caucasian patients with type 2 diabetes, who are in most cases obese or overweight and hyperinsulinemic, liraglutide improves glycemic control with a significant reduction in body weight and a low risk of hypoglycemia[4–9]. On the other hand, in Japanese or Asian subjects with type 2 diabetes, insulin secretion is relatively

decreased by varying degrees[3,10–12]. Liraglutide monotherapy has improved glycemic control in a small number of Phase 2 and Phase 3 clinical trials[13,14]. However, GLP-1 receptor agonists are not always effective. In one study of Caucasian subjects with type 2 diabetes, substitution with exenatide, which is another GLP-1 receptor agonist, for insulin therapy resulted in deterioration in glycemic control in 38% of type 2 diabetic patients, but not in the remaining 62% of patients; however, significant predictors of the efficacy of exenatide could not be shown[15]. The clinical parameters that could discriminate liraglutide-effective patients from liraglutide-ineffective patients have not been identified in Caucasian or in Japanese or other Asian populations.

In this study, we reviewed and analyzed the clinical characteristics of patients with type 2 diabetes to detect parameters predicting the efficacy of liraglutide.

MATERIALS AND METHODS

Patients

We reviewed 23 consecutive patients (nine male, 14 female) with type 2 diabetes admitted to Osaka University Hospital for glycemic control. The mean (±SD) age was 63.5 ± 11.0 years, the mean duration of diabetes was 16.7 ± 8.7 years, and the mean body mass index (BMI) was 27.9 ± 4.8 kg/m². Their

mean levels of hemoglobin A1c (HbA1c) on admission was 9.1 ± 1.5%. Before admission, five patients had been treated with oral antidiabetic drugs (OADs), nine patients had been treated with insulin and nine patients had been treated with OADs plus insulin. OADs included sulfonylurea in seven patients, biguanide in nine patinets, thiazolidinedione in five patients, alpha-glucosidase inhibitor in four patients and phenylalanine derivative in two patients. Antibodies to glutamic acid decarboxylase (GAD) and ketouria were negative in all patients.

Protocol

After admission, all of the patients were treated by diet plus insulin to improve every preprandial plasma glucose level, including fasting plasma glucose (FPG) level, below 150 mg/dL and every postprandial plasma glucose level below 200 mg/dL. OADs were discontinued except biguanide in three patients and thiazolidinedione in two patients. After glycemic control reached the target levels at least for 3 days, their insulin secretion and insulin resistance were evaluated. At the time of evaluation, FPG was 115.1 ± 21.0 mg/dL in liraglutide-effective patients and 119.8 ± 22.9 mg/dL in liraglutide–ineffective patients.

Then, the insulin was replaced by liraglutide (Novo Nordisk, Bagsvaerd, Denmark). The liraglutide dose was increased from 0.3 to 0.9 mg/day in weekly increments of 0.3 mg. The maximum permitted dosage of liraglutide is 0.9 mg/day in Japan. The efficacy of liraglutide was evaluated by examining whether glycemic control was maintained at the target levels mentioned above without additional OAD(s) or insulin administration.

Evaluation of insulin secretion and insulin resistance

Insulin secretion was evaluated by the insulinogenic index (I.I.) of a 75-g OGTT, fasting C-peptide (F-CPR), C-peptide index (CPI)[16] and urine C-peptide (U-CPR). CPI was calculated by the following formula: F-CPR (ng/mL) × 100/FPG (mg/dL).

Insulin resistance was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) in patients treated with neither intermediate-acting insulin nor long-acting insulin. HOMA-IR was calculated by the following formula: FPG (mg/dL) × F-IRI (μU/mL)/405. All these evaluations were done after glycemic control reached the target levels for at least 3 days and before liraglutide therapy started.

Statistics

Data are presented as mean ± standard deviation (SD). Pearson's correlation coefficient analysis was used to assess the relationships between parameters of insulin secretion and duration of type 2 diabetes. A receiver operating characteristic (ROC) curve was used to determine the appropriate cut-off values for parameters of insulin secretion and duration of type 2 diabetes in identifying subjects for whom liraglutide was effective. The Mann–Whitney test was used to compare the clinical characteristics of liraglutide-effective patients and liraglutide-ineffective patients. All statistical analyses were performed with StatView (Statistical Analysis System Inc., Cary, NC, USA) or the SPSS Statistics software package (version 11.0.1J; SPSS, Chicago, IL, USA).

RESULTS

Liraglutide was effective in 13 of 23 patients. The clinical characteristics of the studied subjects are shown in Table 1. There were significant differences in the parameters of insulin secretion, including F-CPR, CPI, I.I. and U-CPR, between liraglutide-effective and -ineffective patients (Table 1, Figure 1). In other words, insulin secretion in liraglutide-effective patients was greater than that of liraglutide-ineffective patients. The duration of type 2 diabetes was also significantly shorter in liraglutide-effective patients than in liraglutide-ineffective patients (Table 1, Figure 1). There was no significant difference in age, BMI, waist circumference (WC), visceral fat area (VFA), HbA1c on

Table 1 | Clinical characteristics of the study subjects with type 2 diabetes for whom liraglutide was effective or ineffective

	Effective	Ineffective	P-value
Number (M/F)	13 (6/7)	10 (3/7)	
Age (years)	62.8 ± 13.2	64.4 ± 8.0	NS
Duration (years)	12.5 ± 8.5	22.0 ± 5.8	0.0042
Body mass index (kg/m^2)	27.3 ± 4.4	28.6 ± 5.5	NS
Waist circumference (cm)	94.3 ± 6.9 (n = 12)	97.0 ± 11.8 (n = 9)	NS
Visceral fat area (cm^2)	144.5 ± 40.5 (n = 11)	147.5 ± 49.5 (n = 8)	NS
HbA1c (%)*	9.1 ± 1.5	9.1 ± 1.6	NS
Fasting plasma glucose (mg/dL)†	115.1 ± 21.0	119.8 ± 22.9	NS
Fasting C-peptide (ng/mL)†	2.1 ± 0.8	1.1 ± 0.8	0.0029
C-peptide index†	1.9 ± 0.8	0.9 ± 0.6	0.0029
Insulinogenic index†	0.26 ± 0.13 (n = 9)	0.05 ± 0.06 (n = 6)	0.0056
Urine C-peptide (μg/day)†	73.1 ± 60.5 (n = 12)	26.7 ± 18.1 (n = 9)	0.044
HOMA-IR†	3.0 ± 1.7 (n = 7)	3.7 ± 3.7 (n = 4)	NS
Insulin dose (unit/kg)†	0.38 ± 0.17	0.56 ± 0.25	NS
Liraglutide dose (mg/day)‡	0.69 ± 0.19	0.75 ± 0.16	NS

Data are mean ± SD. *On admission; †after glycemic control; ‡at the time of evaluation of the efficacy for liraglutide. HOMA-IR, homeostasis model assessment of insulin resistance.
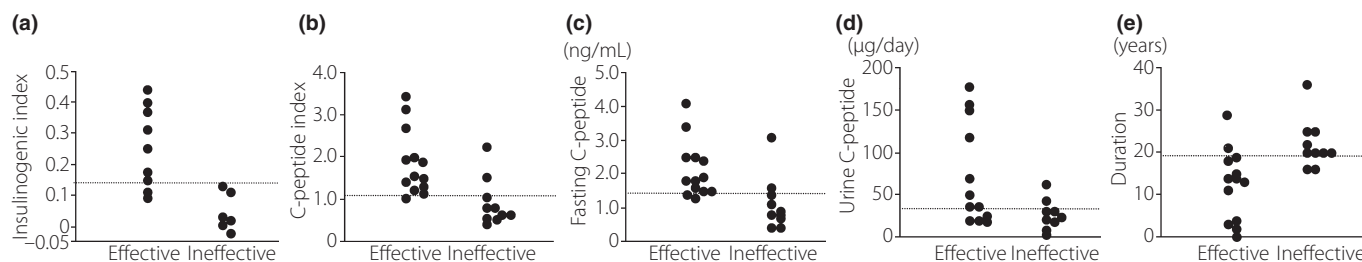
Figure 1 | Clinical parameters in which there were significant differences between liraglutide-effective and liraglutide-ineffective patients with type 2 diabetes. In receiver operating characteristic analyses, the cut-off value for predicting the efficacy of liraglutide was 0.14 for insulinogenic index, 1.1 for C-peptide index, 1.5 ng/mL for fasting C-peptide, 33.3 μg/day for urine C-peptide and 19.5 years for duration of type 2 diabetes.

Table 2 | Characteristics of cut-off values of the clinical parameters for predicting the efficacy of liraglutide in patients with type 2 diabetes

Parameters	Optimal cut-off value	AUC	Sensitivity (%)	Specificity (%)	PV(−) (%)	PV(+) (%)	LR(−)	LR(+)
Insulinogenic index	0.14	0.935	78	100	75	100	0.22	>5.4
C-peptide index	1.1	0.869	92	80	89	86	0.096	4.6
Fasting C-peptide (ng/mL)	1.5	0.869	85	80	80	85	0.19	4.2
Duration (years)	19.5	0.854	85	80	80	85	0.19	4.2
Urine C-peptide (μg/day)	33.3	0.750	67	78	64	80	0.43	3.0

AUC, area under the receiver operating characteristic curve; PV(−), negative predictive value; PV(+), positive predictive value; LR(−), negative likelihood ratio; LR(+), positive likelihood ratio.

admission, HOMA-IR, insulin requirement before changing insulin to liraglutide or liraglutide dose at the time of evaluation of the efficacy of liraglutide. Biguanide was used in two liraglutide-effective patients and in one liraglutide-ineffective patient, while a thiazolidinedione was used in one liraglutide-effective patient and in one liraglutide-ineffective patient. In these patients, biguanide or thiazolidinedione was administered throughout this study. Any other OAD was not used in any patient during insulin therapy and during liraglutide therapy before evaluation of the efficacy of liraglutide. Even when patients who were treated with biguanide or thiazolidinedione along with insulin therapy were excluded, there was no significant difference in HOMA-IR between liraglutide-effective patients ($n = 6$) and -ineffective patients ($n = 3$).

The appropriate cut-off values for predicting the efficacy of liraglutide and AUCs in the ROC analyses are shown in Table 2. Positive and negative predictive values and positive and negative likelihood ratios are also shown (Table 2). All the parameters, including I.I., CPI, F-CPR, duration and U-CPR, had high AUCs and all the cut-off values showed high positive predictive values and high positive likelihood ratios. Among them, I.I. had the highest AUC and its cut-off value (0.14) showed the highest positive predictive value and the highest positive likelihood ratio. CPI had the second, F-CPR had the third, duration had the fourth and U-CPR had the fifth highest AUC, respectively.

DISCUSSION

In this study, we have demonstrated that liraglutide is effective for glycemic control in Japanese type 2 diabetic patients with sustained insulin secretion and shorter duration. All the parameters, including I.I., CPI, F-CPR, duration and U-CPR, were thought to be useful parameters for predicting the efficacy of liraglutide. Among them, I.I. in OGTT was the most valuable parameter in discriminating liraglutide-effective patients from liraglutide-ineffective patients judging from the highest values of AUC and positive likelihood ratio. CPI was the second, F-CPR was the third, duration of type 2 diabetes was the fourth and U-CPR was the fifth, all of which except U-CPR are easier to use than I.I. in the clinical setting. All parameters were evaluated after reduction of glucose toxicity by diet and insulin treatment. These findings may enable us to predict the efficacy of liraglutide, in contrast to a previous report in which exenatide was not effective in patients with lower, but not significantly lower, fasting C-peptide evaluated in a hyperglycemic state[15]. Insulin secretion often deteriorated to varying degrees in Japanese and other Asian patients with type 2 diabetes[3,10–12]. Therefore, evaluation of insulin secretion should be useful to predict the effect before the start of liraglutide therapy.

We should evaluate insulin-secreting capacity not by their physical examination, such as BMI, but by measuring the actual insulin secretion parameters as described in this study. Seven of 10 liraglutide-ineffective patients were obese according to Japanese criteria (BMI ≥ 25). Insulin-secreting capacity is usually sustained in obese patients, but 8 of 10 liraglutide-ineffective patients had already lost their insulin-secreting capacity and were treated with insulin on admission in this study. They might be overweight due to the relative over-dosage of therapeutic insulin.

GLP-1 receptor agonists exert glucose-lowering effects mainly by stimulating glucose-mediated secretion of insulin from beta-cells. Fasting C-peptide-to-glucose ratio, which corresponds to

CPI, is a predictive marker for the fractional beta-cell area of the human pancreas[17]. F-CPR, I.I. and U-CPR after improvement of glycemic control were significantly correlated with CPI ($r = 0.947$, $P < 0.0001$, $r = 0.812$, $P = 0.0002$ and $r = 0.762$, $P < 0.0001$, respectively). Therefore, low CPI, low F-CPR, low I.I. and low U-CPR might reflect reduced beta-cell mass, leading to deteriorated insulin secretion and insufficient efficacy of liraglutide.

The duration of type 2 diabetes was also revealed to be useful in predicting the efficacy of liraglutide in this study. Because the duration was negatively correlated with the parameters of insulin secretion, a shorter duration might mean sustained capacity of insulin secretion, resulting in sufficient efficacy of liraglutide for glycemic control.

In this study, insulin resistance evaluated by HOMA-IR was not a useful marker for predicting the efficacy of liraglutide in patients treated with or without insulin sensitizers. Moreover, there was no significant difference in BMI, WC or VFA, which are supposed to reflect insulin resistance, between liraglutide-effective patients and -ineffective patients, suggesting that the efficacy of liraglutide does not depend on the degree of insulin resistance in patients with type 2 diabetes.

There are some limitations in this study. I.I. of almost all the patients was <0.4, indicating that the early phase of insulin-secreting capacity was deteriorated in them. Some of them had been treated with sulfonylurea, which might affect our results. Moreover, parameters other than insulin-secreting capacity or insulin resistance, such as a ratio of proinsulin to insulin, might be also useful for predicting the efficacy of liraglutide. More detailed and further population-based analyses would be recommended.

In conclusion, insulin secretion evaluated by F-CPR, CPI, I.I., U-CPR and duration of type 2 diabetes were useful parameters for predicting the efficacy of liraglutide in patients with type 2 diabetes. Further prospective studies in these patients after discharge would confirm the usefulness of these parameters.

ACKNOWLEDGEMENTS

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