A higher body mass index attenuates the long-term HbA1c-lowering effects of liraglutide in type 2 diabetes patients treated using sulfonylurea-based therapy

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Abstract

Objective To identify the attenuating factor of glycated hemoglobin (HbA1c)-lowering effects of liraglutide in type 2 diabetes (T2D) patients over the long term.

Methods Forty-six T2D patients received liraglutide-glimepiride combination therapy. Clinical characteristics were compared between the following two subgroups: the relapse group (≥ 0.4 % increase in HbA1c in 48 weeks compared to 12 weeks) and non-relapse group (remaining patients). A glucagon-loading test was performed to evaluate baseline endogenous insulin secretion.

Results In the relapse group, significantly reduced HbA1c, as observed at 12 weeks, tended to increase at 24 and 48 weeks. In the non-relapse group, reduced HbA1c was maintained for 48 weeks. Body weight was decreased at 12 weeks and then recovered at 48 weeks in both groups. Baseline BMI was significantly higher in the relapse group than in the non-relapse group. Age, HbA1c, duration of diabetes, fasting C-peptide, daily glimepiride dose and the duration of glimepiride treatment were comparable between both groups. Multiple logistic regression

analysis revealed that baseline BMI was independently associated with the relapse group.

Conclusion A higher BMI is the leading factor for attenuating long-term glycemic control by liraglutide in T2D patients undergoing sulfonylurea-based therapy.

Keywords BMI · GLP-1 receptor agonist · HbA1c-lowering effect · Liraglutide · Obesity

Introduction

The prevalence of type 2 diabetes (T2D) has been rapidly increasing worldwide, particularly in Asian countries [1]. Obesity is a major risk factor for insulin resistance, which plays a key pathogenic role in T2D [2]. Weight loss constitutes a therapeutic basis for obese T2D patients, yet controlling the appetite and body weight of these patients is often difficult. In addition, treatment with insulin and sulfonylurea often increases adiposity, causing weight gain that further hampers glycemic control [3]. Glucagon-like peptide-1 (GLP-1) is an incretin hormone that exerts a potent blood-glucose-lowering action by inducing insulin secretion in a glucose-dependent manner [4]. Beyond the glucose-lowering effect, GLP-1 also promotes weight loss by delaying gastric emptying and inducing satiety.

Liraglutide is a once-daily human GLP-1 analog that improves glycemic control in T2D patients, lowers the risk of hypoglycemia, and reduces body weight [5, 6].

The position statement of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) recommends GLP-1 receptor agonists as reliable agents for maintaining good glycemic control and weight loss in T2D patients [7]. Several reports have demonstrated that a short duration of diabetes, a high 6-min

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value of C-peptide immunoreactivity (CPR) after glucagon stimulation, and a low BMI at the start of treatment may be predictive of significant liraglutide effects by reducing blood glucose in T2D patients [8–11].

However, no studies have elucidated whether the liraglutide effect on glycemic control can be maintained over longer periods in T2D patients. Recently, Inoue et al. reported that glycemic control was adequately maintained in T2D patients receiving long-term liraglutide treatment over 2 years [12]. Glycated hemoglobin (HbA1c) levels were significantly decreased at 3 months after commencement of liraglutide (7.4 ± 1.1 %); however, there was a tendency for levels to increase at 6, 12, and 24 months (7.8 %). The clinical parameters underlying the relapse of HbA1c after 3 months were not elucidated in that study. Furthermore, in the Liraglutide Effect and Action in Diabetes (LEAD)-2 core trial, a reduction in HbA1c after 2 years of liraglutide treatment was less pronounced than that after 26 weeks (-0.6 vs. -1.0 %, respectively) [13].

The current study aimed to clarify the attenuating factors of the HbA1c-lowering effects of liraglutide over the long term in T2D patients.

Methods

Subjects

The current study was an observational study of T2D patients who were started on liraglutide therapy at Showa University Hospital (Tokyo, Japan) between December 2010 and January 2012. They continued the liraglutide treatment for a period of 1 year. The commencement of liraglutide treatment required discontinuation of all other oral anti-diabetic agents except sulfonylureas. Patients were introduced to liraglutide once daily with a starting dose of 0.3 mg, and the dosage was gradually increased up to 0.9 mg, which is the maximum dose used in Japan. Each treatment was administered by an attending physician. When the current study was started, sulfonylurea was the only agent approved as a combination therapy with liraglutide in Japan. All patients on sulfonylurea were treated with glimepiride at baseline. The glimepiride dose was reduced by half (from 2.0 ± 1.7 mg to 0.5 ± 0.6 mg) to decrease the risk of hypoglycemia when the liraglutide therapy commenced. Patients with type 1 diabetes, gestational diabetes, overt nephropathy (a urine albumin-to-creatinine ratio >300 mg/g, creatinine or glomerular filtration rate <60 ml/min/ 1.73 m²), liver disease, insulin treatment, infections, or malignant tumors were excluded. Patients who were on medications known to affect glycemic control (e.g., corticosteroid) were also excluded.

Diabetic retinopathy was examined by an ophthalmologist. The study was approved by the Institutional Review Board for Clinical Research at the Showa University of Medicine. All patients gave their informed consent to participate.

Study design

T2D patients exhibited insufficient glycemic control with sulfonylurea-based therapy and were administered liraglutide as a second line of therapy after discontinuing antidiabetic agents except glimepiride. As a rule, the glimepiride dosage was not changed during the study.

HbA1c levels were measured before and at 4, 12, 24, 36, and 48 weeks after the initial administration of liraglutide. Body weight was measured at 0, 12, and 48 weeks. Body mass index (BMI) was calculated as body weight (kg)/height² (m²). The glucagon test to assess the residual β -cell function was carried out in the morning after a 10-h fast, just before the administration of liraglutide. The fasting CPR (FCPR) and 6-min CPR were measured. In addition, clinical characteristics were compared between the following two subgroups: the relapse group (HbA1c increased by 0.4 % or more at 48 weeks compared to 12 weeks) and non-relapse group comprising the remaining patients, referring to the previous report by Kubota et al. [14].

Laboratory measurements

Plasma glucose levels were measured using the glucose-oxidase method, and plasma CPR concentrations were measured using the immunoassay (ST E test Tosoh II C-peptide; Tosoh, Tokyo, Japan). The HbA1c (%) values used in this study were estimated using National Glycohemoglobin Standardization Program (NGSP) equivalent values (%) and calculated using the following formula in consideration of the relational expression of HbA1c [Japan Diabetes Society (JDS)] (%) (measured using previous Japanese standard substance and measurement methods) and HbA1c (NGSP): $\text{HbA1c (NGSP)} = \text{HbA1c (JDS)} + 0.4$ % [15].

Statistical analysis

All statistical analyses were performed using JMP[®] 12 (SAS Institute Inc., Cary, NC, USA), and descriptive data were expressed as means $\pm$ standard deviations or as numbers. Continuous variables compared between two groups were analyzed using *t* tests. Logistic regression analysis was used to examine the relationships between variables. Receiver-operating characteristic (ROC) curves were constructed for BMI. Sensitivity, specificity, cutoff points, and areas under the curve (AUC) were calculated. *p* values <0.05 were considered statistically significant.

Results

Baseline clinical characteristics of subjects

Table 1 shows the baseline characteristics of patients in the study. Forty-six T2D patients received the liraglutide-glimepiride combination therapy. Mean age was 56.9 ± 12.3 years, mean BMI was 27.6 ± 4.0 kg/m², and baseline HbA1c was 9.0 ± 2.0 %. The fasting CPR, 6-min CPR, and CPR index for beta cell function were preserved well. The daily glimepiride dose was 2.0 ± 1.7 mg, and the duration of glimepiride treatment was 4.7 ± 3.8 years. Retinopathy, albuminuria, and neuropathy were present in 47.8, 52.2, and 60.9 % patients, respectively. Previous antidiabetic drugs in combination with glimepiride were as follows: biguanides (56.5 %), thiazolidinediones (6.5 %), and α -glucosidase inhibitors (15.2 %).

Changes in HbA1c levels

Figure 1 shows changes in HbA1c levels in all patients in the relapse and non-relapse group. In all patients, HbA1c was significantly decreased at 12 weeks (7.0 ± 1.1 %) with a tendency for levels to increase at 24, 36, and 48 weeks (7.2 ± 1.3 , 7.4 ± 1.5 , and 7.5 ± 1.6 %, respectively). In the relapse group, HbA1c was significantly decreased at 12 weeks (7.6 ± 1.0 %) and returned back to baseline levels at 36 and 48 weeks (8.4 ± 1.3 and 8.6 ± 1.4 %, respectively). In the

Fig. 1 Effect of liraglutide on glycated hemoglobin in all patients and the relapse and non-relapse group. Gray square with a gray line, all patients; black circle with a black line, relapse group (≥ 0.4 % increase in HbA1c in 48 weeks compared to 12 weeks); gray circle with a gray line, non-relapse group (< 0.4 % increase in HbA1c in 48 weeks compared to 12 weeks). Each value represents mean $\pm$ standard deviation. * $p < 0.05$; in paired t test (vs. 0 weeks)

non-relapse group, HbA1c was significantly decreased at 12 weeks (6.4 ± 0.7 %), and this was maintained up to 48 weeks. A significant decrease in HbA1c was observed at 12 weeks compared to baseline HbA1c in both groups, but the reduction in HbA1c at 12 weeks was significantly greater in the non-relapse group than in the relapse group (-2.6 ± 2.1 vs. -1.4 ± 1.9 %, $p < 0.05$, respectively).

Table 1 Baseline characteristics of all patients

N (male/female)	46 (35/11)
Age (years)	56.9 ± 12.3
Height (cm)	165.3 ± 9.9
Body weight (kg)	75.6 ± 12.9
BMI (kg/m ²)	27.6 ± 4.0
Waist circumference (cm)	96.2 ± 14.1
FPG (mg/dl)	163.6 ± 46
Baseline HbA1c (%)	9.0 ± 2.0
Fasting CPR (ng/ml)	2.3 ± 1.1
6 min-CPR (ng/ml)	4.6 ± 1.8
Δ CPR (ng/ml)	2.3 ± 1.2
CPR index	1.5 ± 0.8
Glimepiride dose (mg)	2.0 ± 1.7
Duration of glimepiride (years)	4.7 ± 3.8
Retinopathy	22 (47.8 %)
Nephropathy (UACR ≥ 30 mg/gCr)	24 (52.2 %)
Neuropathy	28 (60.9 %)
Previous anti-diabetic agents BG/TZD/ α -GI	26 (56.5 %)/3 (6.5 %)/7 (15.2 %)

Data are expressed as numbers or mean $\pm$ standard deviation. N, number

BMI body mass index, FPG fasting plasma glucose, CPR C-peptide immunoreactive protein, Δ CPR fasting CPR value subtracted from 6-min CPR, CPR index fasting CPR value divided by FPG, UACR urine albumin-to-creatinine ratio, BG biguanides, TZD thiazolidinediones, α -GI α -glucosidase inhibitors

Changes in body weight

Figure 2 shows changes in body weight from baseline to 48 weeks. In all patients, body weight was significantly decreased at 12 weeks compared to baseline (-1.9 ± 3.2 kg) and subsequently returned to near baseline at 48 weeks. In both subgroups, body weight was also significantly decreased at 12 weeks compared to baseline (-2.0 ± 4.0 and -1.8 ± 2.1 kg, respectively) and subsequently increased back to baseline levels at 48 weeks. Therefore, we analyzed the correlation between Δ HbA1c and Δ body weight from 12 to 48 weeks to exclude any direct effects of increasing body weight on glycemic control in both subgroups. In our supplementary data (Fig. S1), individual changes in HbA1c and body weight from 12 to 48 weeks are shown as a scatter plot. Changes in body weight were not associated with changes in HbA1c from 12 to 48 weeks.

Difference between non-relapse and relapse group

Table 2 shows a comparison of the baseline characteristics and Δ body weight of patients from 12 to 48 weeks in the non-relapse and relapse groups. Baseline BMI in the relapse group was significantly higher than in the non-relapse group (29.4 ± 3.9 vs. 25.7 ± 3.0 kg/m², respectively, $p < 0.05$). There were no significant differences in

sex, age, duration of diabetes, waist circumference, fasting plasma glucose level, HbA1c, dose of glimepiride, or residual insulin secretion in either group. Three patients were pretreated with glimepiride and thiazolidinediones, and all these patients were classified into the relapse group ($p < 0.05$ vs. non-relapse group). The daily dose of biguanides and α -glucosidase inhibitors was not different between the relapse and non-relapse group (1250 ± 365 vs. 1200 ± 268 mg and 0.83 ± 0.15 vs. 0.70 ± 0.17 mg for metformin and voglibose, respectively).

Analysis of the predictive parameters of non-relapse

A multivariate logistic regression analysis was performed using the non-relapse group as the dependent variable and baseline BMI, fasting CPR, HbA1c, dosage of glimepiride, duration of glimepiride, and Δ body weight from 12 to 48 weeks as independent variables (Table 3). The only factor that significantly contributed to non-relapse was BMI ($p < 0.01$, $\chi^2 = 7.66$).

ROC analyses were carried out to determine the BMI cutoff value. AUC was 0.78 ($p < 0.05$), with an estimated cutoff point of 27.9 kg/m², sensitivity of 69.6 %, and specificity of 82.6 % (Fig. 3).

Discussion

In this study, we demonstrated for the first time that a higher BMI (average BMI: 29.4 kg/m²) attenuates the long-term HbA1c-lowering effects of liraglutide in T2D patients treated with sulfonylurea-based therapy.

Previous reports have suggested the usefulness of the 6-min CPR response to glucagon stimulation or CPR index as predictors of the glucose-lowering effect for 12 weeks after liraglutide initiation [9, 16]. These indices for endogenous insulin secretion were similar and indicated a relatively well-preserved β -cell function between the relapse and non-relapse groups. As expected, HbA1c decreased significantly from baseline to 12 weeks, but increased to baseline HbA1c levels at 48 weeks in the relapse group. In other words, endogenous insulin secretion was essential for the improvement of glycemic control at 12 weeks, but the baseline 6-min CPR response to glucagon stimulation and the CPR index could not be predictors of long-term HbA1c-lowering effects of liraglutide in the relapse group.

Several studies have reported that liraglutide leads to weight loss by delaying gastric emptying and inducing satiety [17]. It is well known that body weight reduction after liraglutide initiation is dependent on the baseline body weight of T2D patients [18]. Recently, Inoue et al. reported that a 0.3–0.9-mg dose of liraglutide resulted in a marked weight loss (-3.4 kg from baseline) over 2 years in obese

Fig. 2 Effect of liraglutide on body weight in all patients and the relapse and non-relapse group. Gray square with a gray line, all patients; black circle with a black line, relapse group (≥ 0.4 % increase in HbA1c in 48 weeks compared to 12 weeks); gray triangle with a gray line, non-relapse group (< 0.4 % increase in HbA1c in 48 weeks compared with 12 weeks). Each value represents mean $\pm$ standard deviation. * $p < 0.05$; in paired t test (vs. 0 weeks), ** $p < 0.05$; in paired t test (vs. 12 weeks)

Table 2 Baseline characteristics of patients according to their glycemic control

	Non-relapse group (<0.4 % increase in HbA1c in 48 weeks compared with 12 weeks)	Relapse group (≥ 0.4 % increase in HbA1c in 48 weeks compared with 12 weeks)
<i>N</i> (male/female)	23 (15/8)	23 (19/4)
Age (years)	59.6 $\pm$ 10.2	55.3 $\pm$ 13.7
Height (cm)	166.8 $\pm$ 9.7	163.3 $\pm$ 9.7
Weight (kg)	71.9 $\pm$ 12.9	78.5 $\pm$ 12.0
BMI (kg/m ²)	25.7 $\pm$ 3.0	29.4 $\pm$ 3.9*
Waist circumference (cm)	94.1 $\pm$ 17.2	97.4 $\pm$ 9.7
FPG (mg/dl)	165.2 $\pm$ 43.9	160.8 $\pm$ 47.9
Baseline A1c (%)	8.9 $\pm$ 2.1	8.9 $\pm$ 2.0
Fasting-CPR (ng/ml)	2.0 $\pm$ 0.8	2.5 $\pm$ 1.3
6 min-CPR (ng/ml)	4.3 $\pm$ 1.6	4.8 $\pm$ 2.0
Δ CPR (ng/ml)	2.3 $\pm$ 1.2	2.3 $\pm$ 1.3
CPR index	1.3 $\pm$ 0.6	1.6 $\pm$ 0.8
Glimepiride dose (mg)	1.5 $\pm$ 1.4	2.4 $\pm$ 2.0
Duration of Glimepiride use (years)	3.5 $\pm$ 3.2	5.7 $\pm$ 4.3
Retinopathy	12 (52.2 %)	10 (43.5 %)
Nephropathy (UACR ≥ 30 mg/gCr)	9 (39.1 %)	13 (56.5 %)
Neuropathy	15 (65.2 %)	13 (56.5 %)
Previous anti-diabetic drugs BG/TZD/ α -GI	10 (43.5 %)/0 (0.0 %)/3 (13.0 %)	16 (69.6 %)/3 (13.0 %)*4 (17.4 %)

Non-relapse group: <0.4 % increase in HbA1c in 48 weeks compared with 12 weeks, relapse group: HbA1c ≥ 0.4 % increase in HbA1c in 48 weeks compared with 12 weeks. Data are expressed as numbers or mean $\pm$ standard deviation. *p* values were determined using the unpaired *t* test or χ^2 test for comparisons between the two groups

N number, *BMI* body mass index, *FPG* fasting plasma glucose, *CPR* C-peptide immunoreactive protein, Δ *CPR* fasting CPR value subtracted from 6-min CPR, *UACR* urine albumin to creatinine ratio, *BG* biguanides, *TZD* thiazolidinediones; α -GI, α -glucosidase inhibitors

* Significant difference from non-relapse group

Table 3 Independent predictors of non-relapse (<0.4 % increase in HbA1c in 48 weeks compared with 12 weeks) by multiple stepwise logistic regression analysis

	Estimated value	Standard error	χ^2	<i>p</i> value
Intercept	-12.77	4.50	8.03	0.005
Baseline HbA1c	-0.20	0.28	0.54	0.464
BMI	0.45	0.16	7.66	0.006
Fasting CPR	0.03	0.57	0.00	0.960
Duration of glimepiride	0.24	0.19	1.64	0.201
Glimepiride dose	0.37	0.37	1.02	0.314
Body weight changes 12–48 weeks	0.33	0.19	2.79	0.095

The values show independent contributions to r^2 for each predictor in the model. The dependent variable was non-relapse (<0.4 % increase in HbA1c in 48 weeks compared with 12 weeks). The independent variables were baseline HbA1c, BMI, fasting CPR, duration of SU administration, glimepiride dose, and body weight changes from 12 weeks to 48 weeks

BMI body mass index, *CPR* C-peptide radio-immunoprotein

T2D patients, although more than half of those patients were on insulin therapy [12]. Liraglutide treatment might be more effective at reducing body weight in obese T2D patients who gain weight after the start of insulin therapy. However, apparent weight loss was not observed in the present study. While the cause of the weight gain from week 12 to week 48

is still incomprehensible, it appears that 0.9 mg of liraglutide (the maximal daily dose permitted in Japan) may be insufficient to maintain weight loss over the long term. Liraglutide improves β -cell function as measured by a significant improvement in both first- and second-phase glucose-induced insulin secretion [19] and induces a robust

Fig. 3 Receiver-operating characteristic curve analysis of BMI for predicting non-relapse ($<0.4\%$ increase in HbA1c in 48 weeks compared with 12 weeks). The AUC was 0.7769 with a sensitivity of 69.6 %, specificity was 82.6 %, and cutoff BMI value of 27.94 kg/m²

enhancement of the post-challenge insulin compared with the placebo [20]. In addition, a significant increase in postprandial insulin secretion was observed in sulfonylurea and liraglutide combination therapy compared with sulfonylurea monotherapy [21]. Because hyperinsulinemia and obesity are so closely linked, a lasting insulin secretion by sulfonylurea and liraglutide combination therapy might cancel any body weight reduction after 12 weeks in a relapse group based on high BMI-caused insulin resistance.

To clarify whether relapsing HbA1c after 12 weeks is shown only in a liraglutide–glimepiride combination therapy, we analyzed the change in HbA1c in T2D patients treated with liraglutide monotherapy ($n = 26$, data not shown). In the liraglutide monotherapy group, baseline HbA1c ($10.1 \pm 2.1\%$) was significantly decreased at 12 weeks ($6.1 \pm 0.7\%$) and persisted over the 48-week treatment period. Although endogenous insulin secretion (fasting CPR: 2.2 ± 0.8 ng/ml) and excessive body weight (BMI: 27.1 ± 4.7 kg/m²) in the liraglutide monotherapy group were similar to those in the relapse group of the present study, the difference of change in HbA1c throughout the 48 weeks between both groups is of great interest. Liraglutide suppresses the fasting and postprandial glucagon levels in T2D patients [22]; however, the prandial glucagon level is increased by glimepiride [23]. The opposite effect on glucagon levels between liraglutide and glimepiride may have been attenuated in improved long-term glycemic control in the relapse group despite similar excessive body weight compared with those with liraglutide monotherapy.

Several limitations involved in the present study should be considered. First, there were no data available on endogenous insulin secretion after liraglutide administration; therefore, endogenous hyperinsulinemia could not be proved, leading to the attenuation effect of body weight reduction. Second, the lifestyle changes such as eating behavior and exercise during the study period were not assessed. An increase in HbA1c after 12 weeks in the relapse group might simply be due to an inappropriate lifestyle followed by increasing body weight after 12 weeks. Nonetheless, our conclusions would not be largely changed for the following reason: Baseline BMI was more closely associated with relapse for HbA1c than body weight changes after 12 weeks (Table 3) and body weight changes were not associated with HbA1c changes (supplementary data, Fig. S1). A recent report by Tajiri et al. found an association between a lower baseline score on a lifestyle assessment and relapsing HbA1c levels after sitagliptin treatment [24]. These results suggest that diet and exercise awareness should be persistently reinforced in patients receiving incretin-based therapy. Third, the present study was retrospective and conducted under an open-label design with no control arm, and the number of patients was relatively small. Finally, the HbA1c-lowering effect of liraglutide might be affected by seasonal variation of HbA1c because liraglutide was not administered at the same period.

In summary, we conclude that a higher BMI is associated with inadequate glycemic control in T2D patients treated using sulfonylurea-based therapy. We recommend that baseline BMI as well as endogenous insulin secretion should be considered before liraglutide initiation, particularly in T2D patients undergoing sulfonylurea-based therapy.

Compliance with ethical standards

Ethics policy All procedures followed were in accordance with the Institutional Review Board for Clinical Research at the Showa University of Medicine and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

Conflict of interest Takeshi Yamamoto, Tomoyasu Fukui, Akiko Higuchi, Makoto Ohara, and Toshiyuki Hayashi declare that they have no conflicts of interest. Tsutomu Hirano received a research grant from Eli Lilly Japan K.K. and Takeda Pharmaceutical Co., Ltd., and received lecture fees from Astra Zeneca, Mitsubishi Tanabe Pharma Corp., and MSD K.K.

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