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ORIGINAL

Efficacy and safety of liraglutide monotherapy compared with metformin in Japanese overweight/obese patients with type 2 diabetes

Kumiko Tanaka[1)], Yoshifumi Saisho[1)], Toshihide Kawai[1)], Masami Tanaka[1)], Shu Meguro[1)], Junichiro Irie[1)], Takatoshi Imai[2)], Toshikatsu Shigihara[3)], Jiro Morimoto[4)], Ken Yajima[5)], Yoshihito Atsumi[6)], Izumi Takei[7)] and Hiroshi Itoh[1)]

[1)] *Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*
[2)] *Department of Internal Medicine, Yokohama Municipal Citizens' Hospital, Kanagawa, Japan*
[3)] *Department of Internal Medicine, Eiju General Hospital, Tokyo, Japan*
[4)] *Department of Internal Medicine, Japan Community Health Care Organization Saitama Medical Center, Saitama, Japan*
[5)] *Department of Internal Medicine, Federation of National Public Service Personnel Mutual Aid Associations, Tachikawa Hospital, Tokyo, Japan*
[6)] *Diabetes Center, Eiju General Hospital, Tokyo, Japan*
[7)] *Department of Internal Medicine, Tokyo Dental College Ichikawa General Hospital, Chiba, Japan*

Abstract. There is little information on direct comparison between metformin and glucagon-like peptide-1 (GLP-1) receptor agonists in the Asian population. This study examined the efficacy and safety of liraglutide monotherapy compared with metformin monotherapy in overweight/obese Japanese patients with type 2 diabetes (T2DM). The study was a 24-week, open-labeled, randomized controlled study. Overweight or obese patients with T2DM aged 20-75 years with suboptimal glycemic control were randomized to liraglutide or metformin monotherapy. The primary endpoint was change in HbA1c at week 24. Secondary endpoints included changes in daily glycemic profile, body weight, incidence of hypoglycemia and other adverse events. The study, which was originally planned to enroll 50 subjects in each group, was ended with insufficient recruitment. A total of 46 subjects completed the study, and analysis was conducted in this cohort. Reduction in HbA1c at week 24 was comparable between the metformin (n = 24) and liraglutide (n = 22) groups (-0.95 ± 0.80% *vs*. -0.80 ± 0.88%, $p = 0.77$), while the liraglutide group reached maximal reduction more rapidly than did the metformin group. There was no significant difference in weight gain or incidence of hypoglycemia between the groups. Diarrhea was more frequent in the metformin group, while constipation was more frequent in the liraglutide group. There was no significant difference in treatment satisfaction between the groups. In conclusion, liraglutide and metformin monotherapy showed similar reduction in HbA1c during 24 weeks, with no difference in weight gain or incidence of hypoglycemia in overweight or obese Japanese patients with T2DM.

Key words: Liraglutide, Metformin, Type 2 diabetes, Japanese, Randomized controlled trial

THE PREVALENCE of obesity and type 2 diabetes (T2DM) continues to increase all over the world [1]. Individuals with T2DM have 2- to 3-fold increased risk of cardiovascular disease [2, 3]. Obesity, especially abdominal obesity, itself is also a risk factor for cardiovascular disease, independent of T2DM [4, 5, 6]. Obesity is also associated with various other medical conditions such as hypertension, dyslipidemia, sleep apnea syndrome and cancer [7]. Thus, simultaneous treatment of obesity and T2DM is an urgent issue for obese patients with T2DM.

Metformin is recommended as a first-line oral anti-hyperglycemic agent for the treatment of T2DM in the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines [8]. Treatment with metformin has been shown to have a neutral or even beneficial effect on body weight, in addition to improvement of glycemic control [8]. However, since only a low dose (up to 750 mg/day) of metformin had been approved in Japan until 2010,

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Correspondence to: Yoshifumi Saisho, M.D., Ph.D., Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail: ysaisho@keio.jp

the efficacy and safety of a high dose (up to 2250 mg) of metformin remains to be established in Japanese patients with T2DM.

On the other hand, a meta-analysis of randomized clinical trials has demonstrated significant weight loss as well as improvement of glycemic control and cardiometabolic risk factors in patients with T2DM treated with glucagon-like peptide-1 receptor agonists (GLP-1RA) [9, 10]. It has also been reported that the glucose-lowering effect of incretin therapy is more marked in Asians than in Caucasians [11, 12]. Thus, once-daily administration of a GLP-1RA, liraglutide, could be a first-line treatment for individuals with T2DM, especially those who are overweight or obese, in Japan. Therefore, in this study we evaluated the efficacy and safety of liraglutide monotherapy compared with metformin monotherapy in Japanese overweight/obese patients with T2DM.

Research Design and Methods

Subjects

Overweight or obese patients (*i.e.*, BMI $\geq$ 23.5 kg/m^2 for Asians) with T2DM aged 20-75 years whose glycemic control was suboptimal (HbA1c 6.9-9.4%) were enrolled in this study. To compare liraglutide *vs*. metformin monotherapy, we enrolled only patients treated with lifestyle modification ± an α-glucosidase inhibitor ± low-dose metformin (*i.e.*, 750 mg/day or less) over 3 months, but not those treated with insulin secretagogues such as sulfonylureas and glinides, thiazolidinedione or insulin. The study participants were recruited at six hospitals between September 2010 and September 2013. Exclusion criteria included 1) type 1 diabetes, 2) contraindication to metformin or liraglutide, 3) advanced diabetic retinopathy (i.e., preproliferative or proliferative retinopathy) and 4) pregnancy. The study was approved by the ethical committee of Keio University School of Medicine and registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (http://www.umin.ac.jp/ctr/) as the Keio study for Initial treatment of type 2 Diabetes with Liraglutide versus Metformin (KIND-LM); UMIN000004243. Written informed consent was obtained from all study subjects.

Study protocol

The study was a 24-week, open-labeled, randomized controlled study. Subjects were randomized to either metformin (1500 mg daily or more) or liraglutide monotherapy. Oral hypoglycemic agents that had been used before randomization were discontinued at week 0. The patients were asked to continue lifestyle modification during the study. Metformin was started at an initial dose of 500-750 mg daily, then the dosage was up-titrated weekly to 1500 mg daily. After week 10, the attending physicians were allowed to increase the dosage up to 2250 mg daily, if tolerated. The initial dose of liraglutide was 0.3 mg once daily by subcutaneous injection, and the dosage was up-titrated by 0.3 mg weekly to 0.9 mg daily, which is the maximum dose approved in Japan. The patients were followed monthly for 24 weeks. The primary endpoint was change in HbA1c at week 24.

Estimation of sample size

The study was powered to show superiority in the primary endpoint, HbA1c, at week 24 in the liraglutide group. Based on the phase 2 and 3 studies [13, 14], we estimated HbA1c reduction in the liraglutide group and metformin group to be 1.8% and 1.2%, respectively. In order to detect a difference in HbA1c of 0.6% with SD of 1.0% between the two treatment groups, 50 subjects per group would yield a power of 80% with a 5% two-sided significance level. Assuming a withdrawal rate of 10%, enrollment of 55 subjects per group was planned.

Measurements

Body weight and blood pressure were measured at each visit. Waist circumference at the umbilical level was measured at baseline and week 24. Blood and urine samples were obtained after an overnight fast at each visit. Plasma glucose, HbA1c, insulin, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured using routine automated laboratory methods [15, 16]. HbA1c was measured by high-performance liquid chromatography (HPLC) and expressed as the National Glycohemoglobin Standardized Program (NGSP) value [17].

Serum insulin and C-peptide immunoreactivity (CPR) were measured by EIA. Proinsulin and glucagon were measured by radioimmunoassay (RIA) (Millipore Corp., Darmstadt, Germany). Homeostasis model assessment of insulin resistance (HOMA-IR) or beta cell function (HOMA-β) was calculated using the HOMA-2 calculator (https://www.dtu.ox.ac.uk/homacalculator/). CPR index was calculated as: serum CPR

(ng/mL)/plasma glucose (mg/dL) x 100, as previously described [15].

The following variables were assessed at baseline and week 24. Oxidized LDL was measured by ELISA (Sekisui Medical Corp., Tokyo, Japan) and pentosidine was measured by ELISA (Fushimi Pharmaceutical Co., Ltd., Kagawa, Japan). Urinary excretion rate of 8-hydroxydeoxyguanosine (8-OHdG) was measured by high performance liquid chromatography (HPLC) (in-house prepared solution), and urinary excretion rate of 8-iso-prostaglandin F2alpha (8-iso-PGF2α) was measured by enzyme immunoassay (EIA) (Cayman Chemical Co., Ann Arbor, MI, USA). High-molecular-weight adiponectin was measured by chemiluminescent enzyme immunoassay (CLEIA) (Fuji Rebio Corp., Tokyo, Japan). Leptin was measured by RIA (Millipore Corp.). C-reactive protein (CRP) was measured by nephelometry (Siemens Healthcare Diagnostics Corp., Tokyo, Japan).

Daily glycemic profile

Subjects were asked to conduct 7-point self-monitoring of blood glucose (SMBG) using a Onetouch® UltraVue (LifeScan Inc., Milpitas, CA, USA) at weeks 0 and 24 to assess the daily glycemic profile. Seven-point SMBG was conducted seven times a day; before and 1 h after each meal and at bedtime, for two consecutive days, and the mean of the two days was used for analysis, as previously described [16]. We chose 1 h after meals to assess postprandial glucose level because it has been reported that the postmeal glucose peak in patients with T2DM occurred mostly within 1 h after a meal, and this incremental glucose peak was related to carotid intima-media thickness [18].

Meal Tolerance Test

The standard mixed meal tolerance test (MTT) was performed at baseline and week 24. On the day of MTT, the patients were asked to attend hospital after an overnight fast and instructed to ingest the meal within 15 min. The meal consisted of crackers, pudding and bisque soup (460 kcal; 56.5 g carbohydrate, 18 g fat, 18 g protein, Janefu E460F18, Kewpie Corp., Tokyo, Japan). Plasma glucose, insulin, C-peptide and glucagon were measured before and 60 min after meal ingestion.

Assessment of hypoglycemia, gastrointestinal symptoms and treatment satisfaction

The incidence and severity of hypoglycemia were assessed using a questionnaire completed by the patients at each visit. Hypoglycemia was defined as having hypoglycemic symptoms and/or blood glucose less than 70 mg/dL. Severe hypoglycemia was defined as hypoglycemia needing the assistance of a third party to recover. To evaluate changes in gastrointestinal symptoms, patients were asked to fill in the Gastrointestinal Symptom Rating Scale (GSRS) score [17], a validated survey of gastrointestinal symptoms (abdominal pain, reflux, indigestion, diarrhea, and constipation) at each visit. The patients were also asked to complete the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [19] and the Diabetes Medication Satisfaction Questionnaire (DiabMedSat) [20] to assess treatment satisfaction at weeks 0 and 24.

Statistical analysis

All normally distributed data are presented as mean ± SD in the text and tables and as mean ± standard error (SE) in the figures, while non-normal data are presented as median and interquartile range (IQR). Statistical analyses were performed using SPSS version 22 (IBM, Chicago, IL, USA). Mann-Whitney's U test or Fisher's exact test was used to compare differences between the groups. Wilcoxon signed-rank test was used to analyze the difference in each parameter from baseline. To analyze sensitivity, the longitudinal profile was also analyzed by mixed model repeated measures (MMRM). A p value <0.05 was considered statistically significant.

Results

Enrollment of subjects

Due to insufficient recruitment, the study was ended with the enrollment of a total of 50 subjects. Among the 50 subjects, 3 subjects withdrew their consent before randomization. Then, 47 subjects were randomized into two groups, and one patient was excluded because of protocol violation. Thus, a total of 46 patients (metformin 24, liraglutide 22) completed the study (Fig. 1). Analysis was conducted in this cohort.

Baseline characteristics of study participants

The metformin group (n = 24) and liraglutide group (n = 22) were matched for age (51 ± 11 *vs*. 55 ± 11 years, p = 0.24), sex (male/female) (16/8 *vs*. 13/9, p = 0.59), BMI (28.7 ± 3.6 *vs*. 28.6 ± 4.1 kg/m^2, p = 0.61), duration of diabetes (4.7 ± 3.9 *vs*. 5.6 ± 4.2 years, p = 0.47) and HbA1c (8.0 ± 0.7% *vs*. 7.7 ± 0.7% (64

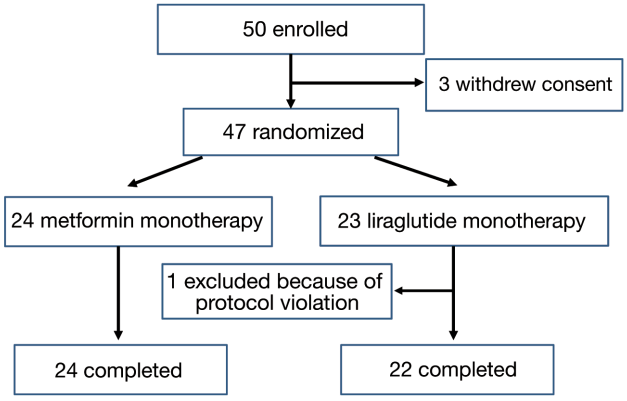

Fig. 1 Patient flow

Table 1 Baseline characteristics of patients

	Metformin	Liraglutide	*p* value
N	24	22	-
Age (years)	51 ± 11	55 ± 11	0.24
Sex (male/female)	16/8	13/9	0.59
BMI (kg/m^2)	28.7 ± 3.7	28.6 ± 4.2	0.61
Waist circumference (cm)	97.3 ± 10.3	96.3 ± 9.4	0.88
Duration of diabetes (years)	4.7 ± 3.9	5.6 ± 4.2	0.47
Systolic blood pressure (mmHg)	136 ± 14	132 ± 14	0.36
Diastolic blood pressure (mmHg)	85 ± 10	82 ± 8	0.22
Fasting plasma glucose (mg/dL)	164 ± 39	163 ± 34	0.88
HbA1c (%)	8.0 ± 0.7	7.7 ± 0.7	0.27
HbA1c (mmol/mol)	64 ± 8	61 ± 8	0.27
LDL-cholesterol (mg/dL)	116 ± 30	119 ± 30	1.00
HDL-cholesterol (mg/dL)	52 ± 12	49 ± 11	0.61
Triglyceride (mg/dL)	204 ± 261	157 ± 71	0.41
Simple retinopathy (%)*	4.2	4.5	0.95
Microalbuminuria (%)**	8.3	9.1	0.93
Prior medication (%)	50.0	63.6	0.35
α-GI (%)	8.3	18.2	0.32
Metformin (%)	50.0	54.5	0.76

α-GI, α-glucosidase inhibitor. * None with preproliferative or proliferative retinopathy. ** None with macroalbuminuria or renal failure.

± 8 *vs*. 61 ± 8 mmol/mol), $p = 0.27$) (Table 1). Prior medication was also comparable between the groups ($p = 0.35$). Duration of prior medication was also similar between the groups (17.3 ± 25.1 *vs*. 14.5 ± 16.4 months, $p = 1.00$).

Changes in HbA1c and daily glycemic profile

The mean daily dose of metformin at week 24 was 1705 ± 342 mg, and liraglutide was up-titrated to 0.9 mg/day in all patients during the study.

HbA1c significantly decreased from 8.0 ± 0.7% to 7.0 ± 0.8% (53 ± 2 mmol/mol) in the metformin group ($p < 0.001$) and from 7.7 ± 0.7% to 6.9 ± 0.9% (52 ± 2 mmol/mol) in the liraglutide group ($p = 0.001$) at week 24 (Fig. 2A). In the metformin group, HbA1c gradually improved during the study, while HbA1c rapidly improved within the first 4 weeks in the liraglutide group. As a result, change in HbA1c at week 4 was significantly greater in the liraglutide group than in the metformin group (-0.56 ± 0.36% *vs*. -0.31 ± 0.29%, $p = 0.02$, Fig. 2B). The change in HbA1c at week 24 was not significantly different between the groups (-0.95 ± 0.80% *vs*. -0.80 ± 0.88%, $p = 0.77$, Fig. 2B). MMRM analysis also confirmed that there was no significant difference in HbA1c reduction at week 24 between the two groups (0.30%, 95% confidence interval -0.09, 0.69, $p = 0.13$). These results did not change in a subpopulation of drug-naïve patients (n = 12 and 8 in metformin and liraglutide group, respectively). In drug-naïve patients, the reduction in HbA1c at week 24 was not significantly different between the groups (-1.28 ± 0.54% *vs*. -1.38 ± 0.39% in metformin *vs*. liraglutide, $p = 1.00$), while the reduction in HbA1c at week 4 was significantly greater in the liraglutide group compared with the metformin group (-0.70 ± 0.39% *vs*. -0.36 ± 0.23%, $p = 0.04$). Furthermore, the results also did not change in a subanalysis of patients with or without prior metformin treatment (reduction in HbA1c at week 24; -0.63 ± 0.90% *vs*. -0.38 ± 0.97% in metformin *vs*. liraglutide, $p = 0.98$ and -1.28 ± 0.54% *vs*. -1.31 ± 0.38%, $p = 0.82$ in patients with and without prior metformin treatment, respectively).

The rate of achievement of HbA1c less than 7% at week 24 was comparable between the groups (62.5% *vs*. 59.1% in metformin *vs*. liraglutide, $p = 0.81$, Fig. 2C). In both groups, daily glycemic profile assessed by 7-point SMBG was significantly improved at all time-points, except for pre-dinner in the metformin group ($p = 0.06$ *vs*. liraglutide) (Fig. 2D).

Changes in body weight and waist circumference

In both groups, there was no significant change in body weight during the study (78.9 ± 16.5 kg at week 0 *vs*. 78.0 ± 17.7 kg at week 24 in metformin, $p = 0.09$, and 76.2 ± 11.6 *vs*. 75.9 ± 11.0 kg in liraglutide, $p = 0.33$). The change in body weight during the study was comparable between the groups (-0.9 ± 2.6 *vs*. -0.3 ± 1.9 kg in metformin *vs*. liraglutide, $p = 0.44$, Fig. 3A). The change in waist circumference during the study was also comparable between the groups (-0.8 ± 5.1

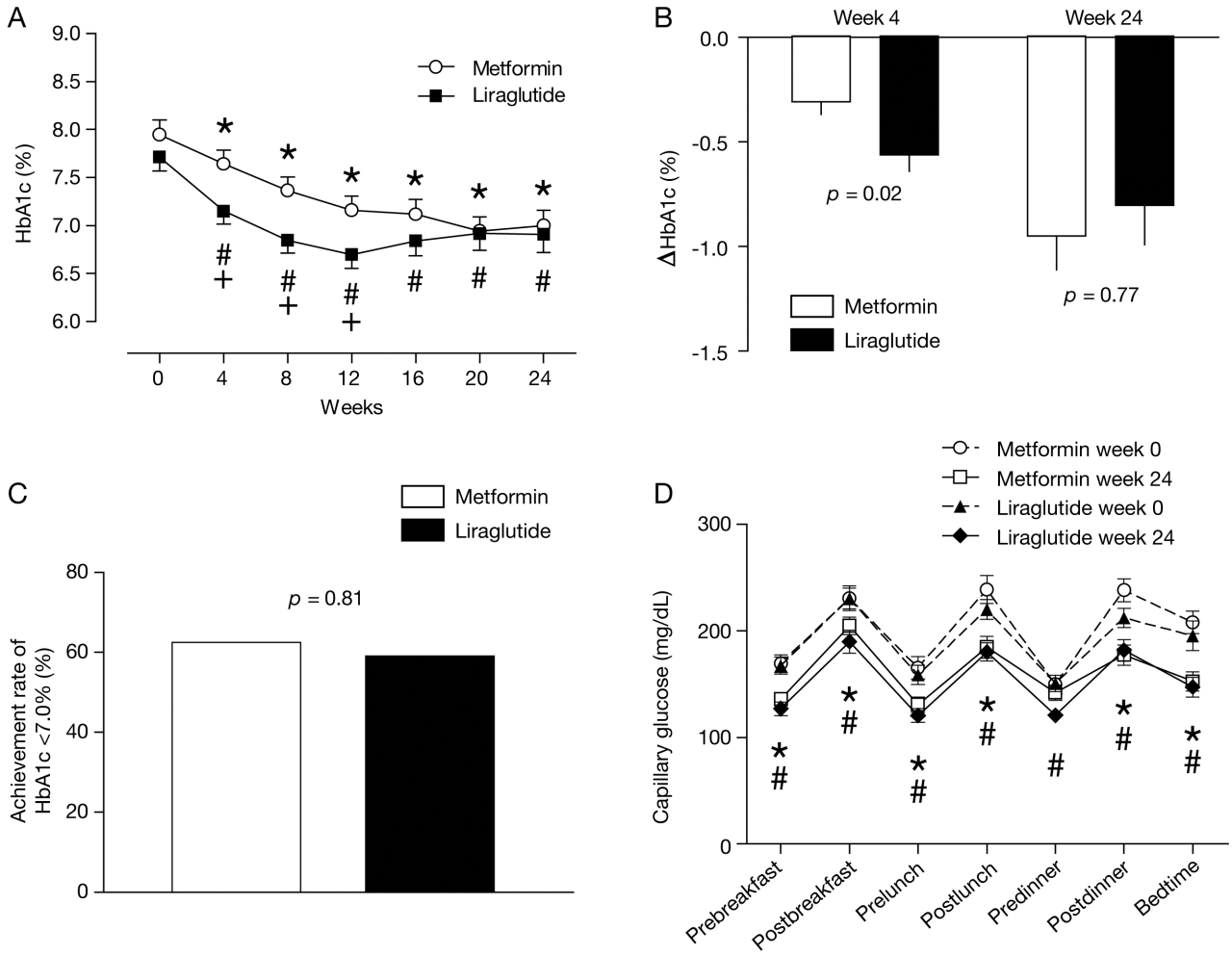

Fig. 2 A) Change in HbA1c during the study. B) Change in HbA1c from baseline at weeks 4 and 24. C) Rate of achievement of HbA1c <7% at week 24. D) Change in daily glycemic profile. * p <0.05 *vs*. baseline in metformin group. # p <0.05 *vs*. baseline in liraglutide group. + p <0.05 vs. metformin group.

vs. -0.1 ± 4.0 cm in metformin *vs*. liraglutide, $p = 0.60$, Fig. 3B).

Meal tolerance test, beta cell function and insulin resistance

The results of MTT are shown in Table 2. Plasma glucose before and 60 min after meal ingestion were significantly improved at week 24 in both groups (all p <0.05). The increment of plasma glucose at 60 min (Δ0-60) was significantly decreased only in the metformin group ($p = 0.02$). CPR index at 0 and 60 min was significantly increased in the liraglutide group at week 24, while HOMA-β and proinsulin to insulin ratio were significantly improved at week 24 in both groups (all p <0.05, Table 2).

Changes in other parameters

Changes in adipokines, inflammatory and oxidative stress markers during the study are shown in Table 3. None of them significantly changed during the study (all p >0.05) except that urinary excretion rate of 8-OHdG was significantly decreased at week 24 in the liraglutide group ($p = 0.02$, Table 3), although there was no significant difference in the urinary excretion rate of 8-OHdG at week 24 between the groups (p = 0.25). There was also no significant change in systolic and diastolic blood pressure and lipid profile during the study in both groups (data not shown).

Hypoglycemia and other adverse events

There was no significant difference in incidence of

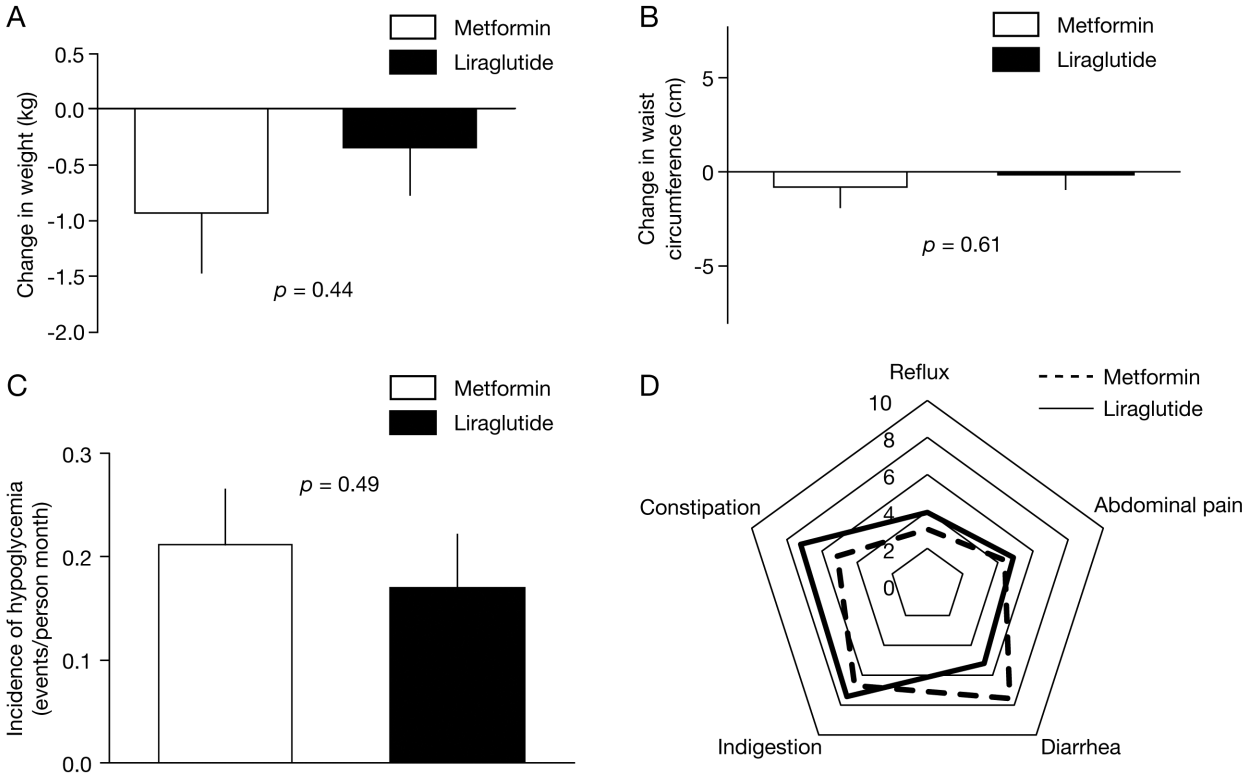

Fig. 3 Changes in body weight (A), waist circumference (B), and incidence of hypoglycemia (C) during the study. D) GSRS score at week 24. GSRS; Gastrointestinal Symptom Rating Scale.

Table 2 Results of meal tolerance test

Week		Metformin		Liraglutide	
		0	24	0	24
Glucose (mg/dL)	0 min	171 ± 42	140 ± 31*	151± 28	133 ± 36*
	60 min	262 ± 55	209 ± 34*	227 ± 27	201 ± 41*
	Δ0-60	90 ± 28	69 ± 22*	76 ± 29	68 ± 38
Insulin (μU/mL)	0 min	13 ± 6	11 ± 6	12 ± 7	23 ± 44
	60 min	36 ± 19	28 ± 10	34 ± 19	51 ± 47
	Δ0-60	23 ± 17	17 ± 12	22 ± 15	23 ± 18
CPR (ng/mL)	0 min	2.6 ± 1.2	2.3 ± 0.9*	2.8 ± 1.3	3.6 ± 3.7$^{\#}$
	60 min	4.7 ± 1.1	4.4 ± 1.3	4.6 ± 1.7	5.5 ± 5.7
	Δ0-60	2.1 ± 1.3	2.2 ± 0.9	1.8 ± 1.1	1.9 ± 1.4
CPR index	0 min	1.6 ± 0.7	1.7 ± 0.6	1.8 ± 0.7	2.5 ± 1.6*$^{\#}$
	60 min	1.9 ± 0.4	2.2 ± 0.7	2.0 ± 0.8	2.8 ± 1.8*
Glucagon (pg/mL)	0 min	82 ± 17	83 ± 24	84 ± 24	84 ± 21
	60 min	98 ± 18	96 ± 26	97 ± 27	94 ± 29
	Δ0-60	16 ± 19	12 ± 20	14 ± 15	10 ± 20
HOMA-β		43.6 (39.4-55.0)	63.7 (40.7-97.7)*	39.6 (28.2-59.3)	65.5 (56.9-93.0)*
HOMA-IR		2.1 (1.2-2.5)	1.5 (1.2-2.5)	1.7 (0.8-2.5)	1.9 (1.1-2.4)
Fasting proinsulin (pmol/L)		25.4 (15.9-49.5)	18.3 (13.0-29.3)*	24.4 (12.5-44.4)	18.2 (12.8-34.4)
Proinsulin/insulin ratio		0.40 (0.27-0.57)	0.33 (0.27-0.40)*	0.36 (0.23-0.55)	0.26 (0.20-0.37)*

* p <0.05 *vs*. week 0. $^{\#}$ p <0.05 *vs*. metformin group. Data are expressed as mean ± SD or median (IQR).

Table 3 Changes in adipokines, inflammatory and oxidative stress markers

	Metformin		Liraglutide	
Week	0	24	0	24
HMW-adiponectin (μg/mL)	2.3 (1.9-2.9)	2.3 (1.5-3.2)	1.8 (1.2-3.0)	2.0 (1.2-3.6)
Leptin (ng/mL)	9.1 (6.9-12.7)	8.5 (5.8-13.5)	9.8 (5.4-16.5)	9.7 (6.8-15.3)
CRP (ng/mL)	1090 (612-1550)	748 (348-1698)	842 (485-1903)	792 (469-1530)
Oxidized LDL (U/L)	117.0 (103.8-150.8)	130.5 (114.8-151.8)	135.0 (117.3-167.5)	135.5 (123.5-156.8)
Pentosidine (μg/mL)	0.031 (0.025-0.043)	0.033 (0.022-0.047)	0.034 (0.025-0.045)	0.030 (0.021-0.039)
Urinary excretion rate of 8-OHdG (ng/mg creatinine)	4.1 (2.8-5.6)	4.7 (3.3-6.0)	4.3 (3.5-6.0)	3.8 (2.8-5.1)*
Urinary excretion rate of 8-iso-PGF2α (pg/mg creatinine)	160.5 (102.5-206.3)	173.0 (128.5-263.5)	133.0 (108.3-190.3)	172.0 (116.3-230.3)

* p <0.05 *vs*. week 0. # p <0.05 *vs*. metformin group. Data are expressed as median (IQR). HMW, high-molecular-weight; CRP, C-reactive protein; LDL, low-density lipoprotein; 8-OHdG, 8-hydroxydeoxyguanosine; 8-iso-PGF2α, 8-iso-prostaglandin F2alpha.

hypoglycemia between the groups (0.2 ± 0.1 *vs*. 0.2 ± 0.1 events/person·month in metformin *vs*. liraglutide, $p = 0.49$), and there was no case of severe hypoglycemia during the study (Fig. 3C). Based on the GSRS score, constipation was more frequent in the liraglutide group than in the metformin group at week 24 (7.2 ± 3.3 *vs*. 5.1 ± 3.2, $p = 0.02$), while diarrhea tended to be more frequent in the metformin group (7.6 ± 5.2 *vs*. 5.2 ± 3.2, $p = 0.10$, Fig. 3D). The incidence of gastrointestinal symptoms was constant throughout the study. There was no incidence of pancreatitis.

Treatment satisfaction

There was no significant change in treatment satisfaction assessed by DTSQ and DiabMedSat during the study in both groups (data not shown, all p >0.05). There was no significant difference in DTSQ and DiabMedSat score at week 24 between the groups (data not shown). There was also no significant difference in each item of DTSQ between the groups at week 24 (data not shown).

Discussion

In this study, treatment with metformin or liraglutide monotherapy resulted in similar HbA1c reduction by 0.8-1% after 6 months in Japanese overweight/obese patients with T2DM. Since metformin is positioned as a first line drug in most guidelines [8, 21, 22], most clinical trials have examined the efficacy of GLP-1RA compared with that of other anti-diabetic medication, and relatively few studies have examined the efficacy of GLP-1RA directly compared with that of metformin.

The efficacy of exenatide extended release (once weekly exenatide) compared with metformin (2000 mg daily) in drug-naïve patients with T2DM has been reported [23]. In that study, a similar reduction in HbA1c was observed in both groups, consistent with our findings. It is of note that the dose of liraglutide in our study (0.9 mg daily, the maximum dose approved in Japan) is less than the usual dose in other countries (*i.e*., 1.2-1.8 mg daily). This is consistent with a previous meta-analysis showing that the efficacy of GLP-1RA is more potent in Asians compared with other ethnicities [12]. More recently, it has been reported that dulaglutide, a once-weekly GLP-1RA, monotherapy showed superior HbA1c reduction compared with metformin [24]. Thus, these results suggest that the glucose-lowering effect of GLP-1RAs is similar or even superior to that of metformin.

The reduction in HbA1c reached a near-maximal level at week 12 in the liraglutide group, while a gradual reduction in HbA1c until 24 weeks was observed in the metformin group. This difference in the time-course of the glucose-lowering effect between liraglutide and metformin was consistent with the findings of previous studies in which other GLP-1RAs were used [23, 24]. This difference may be derived from differences in pharmacokinetic characteristics, mode of action and titration period between the two drugs. While metformin improves hyperglycemia mainly by reducing hepatic glucose production [25], liraglutide acts mainly by enhancing insulin secretion [26]. Rapid improvement of glycemic control within one month after commencing liraglutide treatment has also been confirmed by continuous glucose monitoring [27].

We also assessed the daily glycemic profile by 7-point SMBG. As a result, metformin and liraglu-

tide similarly ameliorated both premeal and postmeal hyperglycemia. It has been reported that long-acting GLP-1RAs such as liraglutide and exenatide extended release reduce premeal and postmeal glycemia similarly, mainly through enhancing insulin secretion, while short-acting GLP-1RAs such as exenatide and lixisenatide predominantly suppress postmeal glycemia through inhibiting gastric emptying [26], which is consistent with our findings.

During this study, neither body weight nor waist circumference decreased significantly in both groups. No significant change in body weight or waist circumference was observed during the study even in the subpopulation of drug-naïve patients (data not shown). This may have been due to the small sample size and insufficient lifestyle modification in the study participants despite asking them to continue their lifestyle modification during the study. Nonetheless, our study suggests that the effect of liraglutide on body weight was comparable to that of metformin in clinical settings. A similar reduction in body weight of ~2 kg with metformin and GLP-1RAs was also reported in previous studies [23, 24].

It has been reported that treatment with GLP-1RAs results in a modest improvement of cardiovascular risk factors such as blood pressure and lipid profile [10, 28, 29]. In this study, blood pressure and lipid profile as well as body weight did not change in either group. On the other hand, it has been reported that exenatide extended release and metformin showed comparable improvement of cardiovascular risk factors as well as body weight [23], suggesting that the improvement of cardiovascular risk factors by GLP-1RA and metformin is mainly mediated by weight reduction. Recently, Rizzo *et al*. reported that the addition of liraglutide (1.2 mg/day) to metformin for 2 months reduced oxidative stress markers in 20 patients with T2DM [30]. Okada *et al*. also reported that liraglutide reduced oxidative stress markers in Japanese patients with T2DM [31]. However, in this study there was no change in adipokines and inflammatory and oxidative stress markers in either group, except that the urinary excretion rate of 8-OHdG was significantly decreased in the liraglutide group. This inconsistency between the studies might be derived from the difference in patients' characteristics, dose of liraglutide, and duration of treatment.

In this study, pre- and postprandial CPR index were significantly increased in the liraglutide group, and HOMA-β and proinsulin to insulin ratio were significantly improved in both groups. The improvement of beta cell function by liraglutide treatment is consistent with previous findings [26, 32, 33, 34]. In addition, the amelioration of hyperglycemia itself might also have contributed to the improvement of beta cell function in both groups. Although we did not evaluate beta cell function after cessation of the drugs, it has been reported that metformin improved beta cell function in non-obese Chinese patients with T2DM [35], suggesting that metformin improves not only insulin sensitivity but also beta cell function, especially in Asians, who are less obese than Caucasians. We did not observe a significant change in fasting and postprandial glucagon levels in either group, which is inconsistent with previous reports showing suppression of glucagon level by GLP-1RAs [26, 32]. This might have been due to differences in patients' characteristics, treatment period or dose of liraglutide between the studies, and also the inaccuracy of current glucagon measurement [36]. On the other hand, HOMA-IR was not significantly changed during the study in either group. Improvement of HOMA-β but not HOMA-IR after either metformin or liraglutide treatment was also reported in other Asian studies [33, 35]. This might have been due to the higher insulin sensitivity in the Asian population compared with other ethnicities [37] and the lack of weight reduction during the study.

The incidence of hypoglycemia was low and was similar between the groups during the study, consistent with previous studies [23, 24]. Gastrointestinal symptoms are well-known adverse events reported with both metformin and GLP-1 RAs [23, 24, 26, 32]. In this study, diarrhea was more frequent in the metformin group, while constipation was more frequent in the liraglutide group. However, the overall incidence of adverse events was similar between the groups, and there was no serious adverse event including severe hypoglycemia during the study.

Although fear or unwillingness to have injections is often considered to decrease treatment satisfaction [38], treatment satisfaction in the liraglutide group was not reduced during the study. It has been reported that treatment with GLP-1RAs improved treatment satisfaction and quality of life in patients with T2DM [39, 40, 41]. Thus, the present and previous studies suggest that treatment with liraglutide does not necessarily worsen treatment satisfaction compared with that with metformin treatment.

The small sample size was a major limitation of

this study in which some differences between the groups might not have been detected due to insufficient statistical power; thus, the results of this study should be confirmed in larger trials. Especially, since this study was originally designed to enroll 100 subjects, it should be stressed that insufficient recruitment might have resulted in failure to detect a difference in HbA1c between the groups. However, to detect a 0.2% difference in HbA1c between the groups, as seen in this cohort, enrollment of 300 subjects in each group would be needed, implying that even if enrollment of 100 subjects had been completed, we might not have been able to find a significant difference in HbA1c reduction between the two groups. Thus, we believe that this information will help in planning further studies. Second, since half of the patients were already being treated with low-dose metformin at study entry, the efficacy of metformin might be underestimated in this study. However, the results were consistent in a subgroup analysis of drug-naïve patients and patients without prior metformin treatment. Neither body weight change nor incidence of adverse events was different between patients with and without prior metformin therapy (data not shown). Furthermore, the proportion of patients with prior metformin treatment was similar between the groups and, although we did not set up a wash-out period for prior treatment for ethical reasons in the clinical practice setting, the study duration of six months was long enough to eliminate the effect of prior metformin treatment. Thus, taking these points together, this possibility of the efficacy of metformin being underestimated is unlikely. Lastly, since we enrolled patients with a relatively short duration of T2DM, the results may be different for patients with a more advanced stage of diabetes. In addition, since the study duration was short, long-term efficacy and safety need to be examined in a further study.

In conclusion, in overweight and obese Japanese patients with T2DM, liraglutide and metformin monotherapy showed a similar reduction in HbA1c during 24 weeks, with no difference in weight gain or incidence of hypoglycemia. Diarrhea was more frequent with metformin therapy, while constipation was more frequent with liraglutide. These findings will be useful for selecting anti-diabetic medication for overweight/obese Japanese patients with T2DM and, when considering the cost, support metformin as a first-line drug in overweight/obese Japanese patients with T2DM, unless contraindicated.

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Author Contributions

K.T. and Y.S. researched data and wrote the manuscript. K.T., Y.S., T.K., M.T., S.M., J.I., T.I., T.S., J.M., K.Y., Y.A., I. T. and H.I. contributed to the discussion, and reviewed and edited the manuscript. Y.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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