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CLINICAL TRIAL

Insulin–glucagon-like peptide-1 receptor agonist relay and glucagon-like peptide-1 receptor agonist first regimens in individuals with type 2 diabetes: A randomized, open-label trial study

Yumie Takeshita, Yuki Kita, Takeo Tanaka, Hisanori Goto, Yujiro Nakano, Chisato Teramura, Yasufumi Enyama, Toshinari Takamura*, the Establishment of Rationale for Antiaging Diabetic Medicine (ERA-DM) Study Group†

Department of Endocrinology and Metabolism, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Ishikawa, Japan

Keywords
Glucagon-like peptide-1 receptor agonists, Glucose toxicity, Insulin–glucagon-like peptide-1 receptor agonist relay regimen

***Correspondence**
Toshinari Takamura
Tel.: +81-76-265-2711
Fax: +81-76-234-4214
E-mail address:
ttakamura@med.kanazawa-u.ac.jp

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Clinical Trial Registry
Efficacy and Safety of GLP-1 first therapy compared with Insulin GLP-1 relay therapy in type 2 diabetes with inadequate glucose control: a randomized, open-label, multicenter parallelgroup study (UMIN000014140).

ABSTRACT

Aims/Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) might be less effective in patients with severe hyperglycemia, because hyperglycemia downregulated the GLP-1 receptor in an animal study. To examine this hypothesis clinically, we compared the glucose-lowering effects of GLP-1 receptor agonist liraglutide with and without prior glycemic control.

Materials and Methods: In an open-label, parallel trial, participants with poorly controlled type 2 diabetes were recruited and randomized to receive once-daily insulin therapy, degludec (Insulin–GLP-1 RA relay group, mean 16.8 ± 11.4 IU/day), for 12 weeks and then liraglutide for 12 weeks or subcutaneous injections of GLP-1 RA, liraglutide (GLP-1 RA first group, 0.9 mg), for 24 weeks. The primary efficacy end-points consisted of changes in the levels of fasting plasma glucose and glycated hemoglobin (HbA1c).

Results: The median fasting plasma glucose and HbA1c before the study were 210.0 mg/dL and 9.8%, respectively. The levels of fasting plasma glucose and HbA1c significantly decreased in the Insulin–GLP-1 RA relay group ($P < 0.001$) and GLP-1 RA first group ($P < 0.001$) by week 24, although no intergroup differences were observed. The reduction of HbA1c in the Insulin–GLP-1 RA relay group tended to be larger than that in the GLP-1 RA first group in the lowest CPR (C-peptide immunoreactivity) quartile ($P = 0.072$). The adverse events consisted of gastrointestinal problems, followed by hypoglycemia.

Conclusions: The GLP-1 receptor agonist is overall effective without prior glycemic control with insulin in participants with poorly controlled type 2 diabetes. However, in participants with insulinopenic type 2 diabetes, prior glycemic control with insulin might overcome glucose toxicity-induced GLP-1 resistance.

INTRODUCTION

Emerging evidence suggests that treatment with glucagon-like peptide-1 (GLP-1) receptor agonists (RA) has beneficial effects on cardiovascular and mortality outcomes in patients with type 2 diabetes[1,2]. Recent guidelines recommend starting GLP-1 RA among patients with type 2 diabetes who have established atherosclerotic cardiovascular diseases as part of glycemic management[3]. However, the clinical guidelines consistently recommend that the early introduction of insulin for inadequately controlled type 2 diabetes patients[3,4] especially with ongoing

† See Establishment of Rationale for Antiaging Diabetic Medicine (ERA-DM) Study Group in Acknowledgments.

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catabolic features, such as weight loss and ketosis if symptoms of hyperglycemia are present, or when glycated hemoglobin (HbA1c) levels >10% (86 mmol/mol) or blood glucose levels ≥300 mg/dL (16.7 mmol/L)[3].

In the meta-analysis[5] of the Liraglutide Effect and Action in Diabetes 5 (LEAD-5) study[6] and Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3)[7] by baseline HbA1c quartile between 7.0 and 11.0%, HbA1c values decreased approximately in parallel, with numerically greater reductions in GLP-1RAs than insulin in all quartiles. In contrast, GLP-1 RAs reduce fasting plasma glucose levels to a lesser extent in the highest HbA1c quartiles than basal insulin[5–7], suggesting that GLP-1RA is less effective in reducing fasting plasma glucose in patients with severe hyperglycemia. Indeed, insulin responses to GLP-1RA are substantially reduced in participants with type 2 diabetes compared with non-diabetic control participants[8]. The near-normalization of blood glucose for 4 weeks by intensive insulin therapy improves b-cell responsiveness to GLP-1[9]. In a single-arm study, GLP-1 RA liraglutide maintained glycemic control subsequent to intensive insulin therapy[10]. The incretin effect in participants with type 2 diabetes is reported to be reduced because of a defect in b-cell sensitivity to GLP-1 in humans[11]. This phenomenon might be partly explained by the finding that hyperglycemia downregulates the GLP-1 receptor, which is restored by glucose normalization with phlorizin, in the b-cells in partially pancreatomized rats and *db*/*db* mice[12]. However, no past studies have ever directly tested the involvement of glucose toxicity-mediated GLP-1 resistance. Therefore, we hypothesized that eliminating the glucose toxicity with insulin therapy might be a solution to the hyperglycemia-associated GLP-1 resistance. To test this hypothesis, we evaluated the effect of prior insulin therapy on GLP-1 resistance to achieve adequate glycemic goals. The present study questions which of 'Insulin–GLP-1 RA relay regimen' or 'GLP-1 RA first regimen' is a better treatment option for type 2 diabetes under glucose toxicity states.

MATERIALS AND METHODS

Study design

This was a 24-week, randomized, open-label, parallel-group trial carried out at seven hospitals in Japan between 16 April 2014 and 30 May 2019. This study was designed in accordance with the principles stated in the Declaration of Helsinki. The protocol was reviewed and approved by the institutional review board of each study site (Innovative Clinical Research Center, Kanazawa University, approval number; 2013-081 [1538], 16 April 2014).

Participants

The inclusion criteria consisted of the following: (i) being aged ≥20 years; (ii) having type 2 diabetes mellitus that was poorly controlled (HbA1c levels ≥8.0% 12 weeks before screening); and (iii) having received diet therapy and/or treatment with oral antihyperglycemic drugs for ≥12 weeks. The exclusion criteria consisted of the following: (i) having hypersensitivity or a contraindication to liraglutide or insulin treatment, degludec; (ii) having a medical history and/or complications from diabetic ketoacidosis or severe hypoglycemia; (iii) experiencing severe infection or trauma pre-/post-surgery; (iv) receiving insulin or GLP-1 RA therapy 4 weeks before screening; (v) receiving glucocorticoid therapy; (vi) having poorly controlled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg); (vii) having severe retinopathy; (viii) having a medical history and/or complications from chronic conditions not suitable for the study (e.g., cancer, ischemic heart disease and heart failure); (ix) being pregnant or breastfeeding; and (x) having psychiatric or psychosocial conditions that preclude participation, as assessed by the investigators. Before participation, all eligible individuals provided written informed consent.

Randomization and masking

Participants were randomized in a 1:1 ratio using a computer-generated randomization sequence to the Insulin–GLP-1 RA relay group or GLP-1 RA first group. As this was an open-label trial, no one (participants, investigators and site staff) was masked to the treatment allocation.

Procedures

This was a therapeutic intervention wherein participants received subcutaneous injections of either 0.9 mg liraglutide (Victoza® Subcutaneous Injection; Novo Nordisk, Tokyo, Japan; GLP-1 RA first group) for 24 weeks or insulin degludec (Tresiba® Novo Nordisk; Insulin–GLP-1 RA relay group) once per day for 12 weeks, followed by injections of liraglutide once at bedtime for 12 weeks (Figure S1). Liraglutide injected subcutaneously with a pen device was started at 0.3 mg/day, and escalated by 0.3 mg/3 days to 0.9 mg/day (maximum allowable dosage in Japan). The initiation and titration of degludec were modified according to past studies[13,14], and a diabetes treatment guide published by the Japan Diabetes Society[15]. The starting doses for insulin degludec were 4 IU at bedtime. Using the self-report data on glucose monitoring at several times including FPG and pre-meal glucose values, target glycemic levels were pre-meal glucose values of 80–110 mg/dL, the investigators and participants carried out daily insulin dose titrations. If participants were currently taking oral hypoglycemic agents, they continued with their baseline doses throughout the study, except for dipeptidyl peptidase-4 inhibitors. Dipeptidyl peptidase-4 inhibitors were stopped after intervention in both groups. The ingestion of any other antihyperglycemic medications was prohibited.

During the study period, all participants underwent nutritional and exercise counseling provided by experienced practitioners. In brief, each individual was prescribed a diet to maintain or achieve a body mass index (BMI) of 22:30 kcal/kg/day, 50–60% kcal from carbohydrates, 20–30% kcal from fat and 15–20% kcal from protein. All participants underwent exercise counseling (5–6 metabolic equivalent estimations for 30 min daily) during the study.

Clinical end-points

The primary clinical end-points were evaluated at week 24, and consisted of changes in the levels of FPG, 1,5-anhydroglucitol and HbA1c from baseline.

The secondary clinical end-points were evaluated at week 24, and consisted of changes in blood pressure, heart rate, laboratory parameters, treatment satisfaction, safety and tolerability. Specifically, endothelial function was assessed as the reactive hyperemia index and measured using the EndoPAT 2000 (Itamar Medical, Caesarea, Israel)[16]. As the additional end-point, for HbA1c levels particularly, participants were stratified into quartiles (Q1, 7.6–8.7%; Q2, 8.8–9.6%; Q3, 9.7–10.9%; Q4, 11.0–16.5%) according to baseline HbA1c levels to determine their influence on the treatment outcomes. Treatment satisfaction was evaluated using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)[17]. The overall treatment satisfaction score was calculated as the sum of DTSQ items 1 (Satisfaction), 4 (Convenience), 5 (Flexibility), 6 (Understanding), 7 (Recommend to others) and 8 (Wish to continue).

Finally, safety and tolerability were surveyed on all participants who received at least one dose of the study medication (the full analysis set [FAS]), and assessed by reviewing the number of general adverse, hypoglycemic and hyperglycemic events, frequency of treatment discontinuations, bodyweight, BMI, waist circumference, and urinary ketone levels.

Statistical analysis

The sample size required to detect a −0.9% and −1.24% change in HbA1c levels among the GLP-1 RA first and Insulin–GLP-1 RA relay groups, respectively, with a power of 80% ($\alpha = 0.05$, one-tailed; $\beta = 0.20$) and standardized effect size of 0.6 was 50 participants per group[18,19]. Considering a dropout rate of 10–15%, we aimed to recruit 120 participants.

The results are expressed as the median (interquartile range). The analyses were carried out on the FAS and a per protocol set up to week 24 using the Wilcoxon signed-rank test for intergroup comparisons, and Student's *t*-test or the Mann–Whitney *U*-test for intragroup comparisons. The Statistical Package for the Social Sciences (version 25.0; SPSS, Chicago, IL, USA) was used to carry out the statistical tests; *P*-values <0.05 showed significance.

This study was registered at the University Hospital Medical Information Network (UMIN000014140). The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Participant characteristics

In total, 120 individuals participated in the study ($n = 60$ in the Insulin–GLP-1 RA relay group, $n = 60$ in the GLP-1 RA first group). Of these, 91 took the study medication up to week 24, whereas 13 discontinued it due to an adverse event or withdrew participation ($n = 3$ in the Insulin–GLP-1 RA relay group, $n = 1$ in the GLP-1 RA first group). During follow up, 12 participants were lost ($n = 3$ in the Insulin–GLP-1 RA relay group, $n = 9$ in the GLP-1 RA first group; Figure S2). The groups were well balanced with respect to baseline demographics and disease characteristics both in FAS and PSS (Table S1). The median age of the participants in FAS was 61.0 years; BMI, 25.8 kg/m^2; diabetes duration, 4.0 years; and baseline levels for FPG, HbA1c and CPR, 210.0 mg/dL, 9.8% (8.8–11.1%) and 2.2 ng/mL, respectively. The percentage of newly diagnosed with diabetes was 33.6% (39 participants). Microalbuminuria was present in 17 out of 116 for this study. No study participant experienced macroalbuminuria. The participants have no or mild diabetic complications, such as diabetic nephropathy. The average insulin dose at 12 weeks in FAS given to the Insulin–GLP-1 RA relay group was 16.8 ± 11.4 IU/day (0.26 ± 0.17 kg/IU/day).

Glucose metabolism

At 24 weeks, the FPG levels significantly decreased from baseline for the Insulin–GLP-1 RA relay group (215.0–126.0 mg/dL, $P < 0.001$) and GLP-1 RA first group (204.0–131.5 mg/dL, $P < 0.001$), with no significant differences between groups (−68.0 [−145.0 to −12.0] mg/dL in the Insulin–GLP-1 RA relay group, −43.0 [−116.0 to −8.0] mg/dL in the GLP-1 RA first group, $P = 0.155$). Similarly, the HbA1c levels significantly decreased from baseline for the Insulin–GLP-1 RA relay group (9.8–6.5%, $P < 0.001$) and the GLP-1 RA first group (9.7–6.8%, $P < 0.001$), with no significant differences between groups (−2.8% [−4.2 to −1.3] in the Insulin–GLP-1 RA relay group, −2.1% [−4.0 to −0.7] in the GLP-1 RA first group, $P = 0.286$). The differences between the groups for these primary clinical outcomes were unremarkable (Table 1). As 55 out of 116 participants (47.4%) did not take any anti-diabetes medications, we examined the subanalysis between with and without antidiabetes medications (Table S7). Both in the Insulin–GLP-1 RA relay group and GLP-1 RA first group, there were no significant differences in FPG and HbA1c changes between participants with and without prior antidiabetes medications. In addition, the proportion of participants who attained the HbA1c level (HbA1c <7.0%) from FAS was 61.0% in the Insulin–GLP-1 RA relay group and 47.4% in the GLP-1 RA first group, with no significant differences between groups ($P = 0.140$).

At 12 weeks, the levels of FPG, HbA1c and 1,5-anhydroglucitol were significantly reduced in the Insulin–GLP-1 RA relay group (215.0–121.0 mg/dL, 9.8–7.1% and 2.4–7.4 μg/mL, $P < 0.001$ for all) and the GLP-1 RA first group (204.0–126.0 mg/dL, 9.7–7.1% and 2.2–8.7 μg/mL, $P < 0.001$ for all), although there were no significant differences between them (−60.0 [−123.0 to −9.0] mg/dL, −2.5% [−3.5 to −1.0], and 3.8 [0.0–9.8] μg/mL in the Insulin–GLP-1 RA relay group, −39.0 [−102.0 to −13.0] mg/dL, −1.7 [−3.9 to −0.4] % and 5.5 [0.0–13.1] μg/mL in the GLP-1 RA first group, $P = 0.286$, 0.284, and 0.326; Table S3).

Table 1 | Changes in the characteristics of patients between baseline and 24 weeks

	Insulin–GLP-1 RA relay			GLP-1 RA first			
	Before	24 weeks	*P**	Before	24 weeks	*P**	*P***
Fasting plasma glucose (mg/dL)	215.0 (152.5–299.0)	126.0 (99.0–148.0)	0.000	204.0 (157.8–252.5)	131.5 (108.0–153.3)	0.000	0.155
Hemoglobin A1c (%)	9.8 (9.0–11.2)	6.5 (6.0–7.5)	0.000	9.7 (8.8–11.0)	6.8 (5.9–8.1)	0.000	0.286
1,5-Anhydroglucitol (μg/mL)	2.4 (1.1–5.0)	9.4 (4.1–16.0)	0.000	2.2 (1.4–4.1)	9.1 (2.6–15.7)	0.000	0.844
C-peptide immunoreactivity (ng/mL)	2.0 (1.4–2.7)	2.2 (1.6–3.2)	0.062	2.4 (1.5–3.0)	2.6 (1.8–3.9)	0.008	0.535
Bodyweight (kg)	65.4 (56.6–73.9)	63.1 (56.5–71.6)	0.010	70.1 (60.2–83.8)	67.4 (58.0–82.5)	0.007	0.375
Body mass index (kg/m^2)	25.1 (22.3–28.6)	24.2 (21.1–26.9)	0.003	26.2 (23.3–30.1)	25.3 (22.9–30.7)	0.004	0.504
Waist circumference (cm)	91.0 (82.0–101.0)	86.5 (81.0–94.0)	0.000	94.8 (85.9–103.6)	91.8 (81.0–101.0)	0.000	0.747
Systolic blood pressure (mmHg)	125.0 (114.0–139.0)	126.0 (116.0–138.0)	0.456	127.0 (118.5–138.0)	132.0 (124.0–140.0)	0.072	0.649
Diastolic blood pressure (mmHg)	76.0 (68.0–86.0)	78.0 (70.0–84.0)	0.729	76.0 (68.0–84.0)	78.0 (67.0–89.0)	0.184	0.439
Heart rate (b.p.m.)	77.0 (69.0–86.0)	78.0 (68.0–86.0)	0.892	76.5 (69.3–87.5)	78.0 (70.0–85.0)	0.789	0.732
White blood cell count (/mL)	6750.0 (5560.0–8010.0)	5670.0 (4900.0–7140.0)	0.000	6545.0 (5222.5–7502.5)	5810.0 (4810.0–7180.0)	0.017	0.435
Aspartate transaminase (IU/L)	21.0 (17.0–31.0)	19.0 (15.0–24.0)	0.061	22.5 (17.0–37.3)	21.0 (17.0–25.0)	0.303	0.608
Alanine aminotransferase (IU/L)	27.0 (18.0–49.0)	22.0 (15.0–31.0)	0.002	28.5 (18.3–60.0)	24.0 (18.0–37.0)	0.249	0.146
Alkaline phosphatase (IU/L)	262.0 (219.0–339.0)	226.0 (186.0–291.0)	0.004	249.0 (200.3–327.5)	233.0 (187.0–271.0)	0.014	0.867
Serum calcium (mg/dL)	9.5 (9.2–9.7)	9.5 (9.2–9.8)	0.571	9.4 (9.1–9.7)	9.5 (9.3–9.9)	0.133	0.419
Serum phosphorus (mg/dL)	3.5 (2.9–3.8)	3.3 (3.0–3.8)	0.736	3.2 (2.9–3.7)	3.5 (3.1–3.8)	0.050	0.624
Bone alkaline phosphatase (IU/L)	13.8 (11.0–17.9)	12.7 (9.3–17.0)	0.993	13.3 (11.2–16.9)	12.8 (10.8–15.7)	0.637	0.639
Creatinine (mg/dL)	0.70 (0.50–0.80)	0.70 (0.6–0.8)	0.118	0.60 (0.5–0.7)	0.70 (0.50–0.80)	0.013	0.462
Uric acid (mg/dL)	5.0 (3.9–5.8)	5.1 (4.2–6.2)	0.363	5.0 (3.7–6.3)	5.6 (4.3–7.1)	0.000	0.016
Total cholesterol (mg/dL)	175.0 (157.0–206.0)	178.0 (151.0–207.0)	0.480	192.5 (173.3–217.0)	192.0 (168.0–223.0)	0.760	0.834
Triglycerides (mg/dL)	136.0 (94.0–241.0)	96.0 (78.0–161.0)	0.039	170.5 (98.3–247.0)	112.0 (78.0–191.0)	0.006	0.953
High-density lipoprotein cholesterol (mg/dL)	42.0 (35.0–54.0)	46.0 (42.0–57.0)	0.001	45.0 (36.5–52.0)	48.0 (38.0–64.0)	0.015	0.836
Urinary albumin excretion (mg/gCr)	0.8 (0.5–2.3)	1.1 (0.7–2.3)	0.662	1.1 (0.0–3.0)	1.8 (0.5–5.7)	0.308	0.322
Cystatin C (mg/L)	0.89 (0.80–1.10)	0.89 (0.80–1.13)	0.462	0.88 (0.78–1.02)	0.90 (0.80–1.00)	0.570	0.128
Reactive hyperemia index	1.53 (1.35–1.87)	1.68 (1.46–1.99)	0.043	1.58 (1.40–2.18)	1.61 (1.40–2.33)	0.231	0.796

All values are the median (interquartile range). **P*-value for the intragroup comparison (baseline vs end-point); ***P*-value for the intergroup comparison (change from baseline between groups). GLP-1 RA first, glucagon-like peptide-1 receptor agonist first group; Insulin–GLP-1 RA, receive once-daily insulin therapy, degludec, for 12 weeks and then liraglutide for 12 weeks relay.

From per protocol set, the FPG levels at 24 weeks significantly decreased from baseline for the Insulin–GLP-1 RA relay group (219.0–115.0 mg/dL, $P < 0.001$) and GLP-1 RA first group (197.0–129.0 mg/dL, $P < 0.001$), with no significant differences between groups (−84.5 mg/dL in the Insulin–GLP-1 RA relay group, −48.0 mg/dL in the GLP-1 RA first group, $P = 0.117$). The reduction of HbA1c in the Insulin–GLP-1 RA relay group was relatively larger than that in the GLP-1 RA first group (−3.3% in the Insulin–GLP-1 RA relay group, −2.2% in the GLP-1 RA first group, $P = 0.055$; Table S2). The proportion of participants who attained the HbA1c level (HbA1c <7.0%) from per protocol set is 72.3% in the Insulin–GLP-1 RA relay group and 56.5% in the GLP-1 RA first group, with no significant differences between groups ($P = 0.173$).

Metabolic profile

For both groups, bodyweight, BMI, waist circumference, white blood cell count, and alkaline phosphatase and triglyceride levels significantly decreased, whereas the high-density lipoprotein level significantly increased. For the GLP-1 RA first group, the uric acid levels significantly increased, whereas in the Insulin–GLP-1 RA relay group, the changes were unremarkable. Alanine aminotransferase levels significantly decreased in the Insulin–GLP-1 RA relay group, but not in the GLP-1 RA first group, with no significant difference between the groups. Also, reactive hyperemia index significantly increased in the Insulin–GLP-1 RA relay group, but not in the GLP-1 RA first group, with no significant difference between the groups (Table 1).

At 12 and 24 weeks, no differences in the HbA1c across all baseline HbA1c quartiles were observed between the Insulin–GLP-1 RA relay group and the GLP-1 RA first group (Figure 1; Table 2). There was no association between HbA1c quartiles and insulin dose by the Kruskal–Wallis test ($P = 0.230$).

Each treatment satisfaction score of DTSQ (item 1, 4, 5, 6, 7 and 8) significantly increased for both groups, with no significant differences between the groups. The ratings for the perceived frequency of hyperglycemia or hypoglycemia were also comparable for all participants throughout the study period (Table S4). The median total DTSQ scores for the Insulin–GLP-1 RA relay group and the GLP-1 RA first group were 22.0 and 22.0, respectively, at baseline and 29.0 and 30.0, respectively, at the end of the study. The total DTSQ scores were significantly increased in both groups, with no significant differences between the groups.

Among subanalysis of the changes in HbA1c and FPG according to baseline CPR quartile, there were no significant differences in baseline HbA1c and FPG between the groups, except for baseline HbA1c in the lowest CPR quartile ($P = 0.022$; Table S5). There was no association between CPR quartiles and insulin dose by the Kruskal–Wallis test ($P = 0.432$). The reduction of HbA1c in the Insulin–GLP-1 RA relay group tended to be larger than that in the GLP-1 RA first group in the lowest CPR quartile ($P = 0.072$).

Among subanalysis of the changes in HbA1c and FPG according to baseline BMI quartile, there were no significant differences in baseline HbA1c and FPG between the groups (Table S6). There was no association between BMI quartiles and insulin dose by the Kruskal–Wallis test ($P = 0.290$). No differences in the FPG and HbA1c across all baseline BMI quartiles were observed between the Insulin–GLP-1 RA relay group and the GLP-1 RA first groups.

Adverse events

With regard to adverse events, gastrointestinal issues, such as nausea, abdominal distension, constipation and diarrhea, were the most common and occurred more frequently in the GLP-1 RA first group than in the Insulin–GLP-1 RA relay group ($n = 15$, 26% vs $n = 6$, 10%), followed by hypoglycemia in the Insulin–GLP-1 RA relay group ($n = 5$, 8%). Because of this, nine participants ($n = 7$ in the Insulin–GLP-1 RA relay group, $n = 2$ in the GLP-1 RA first group) wanted to discontinue treatment; thus, the dose of liraglutide was reduced to 0.3 mg for one participant and 0.6 mg for two participants according to the physician's instruction. For two individuals in the Insulin–GLP-1 RA relay group who experienced pneumonia and hyperglycemia, degludec was replaced with intensive insulin therapy (Table 3).

DISCUSSION

The present study is the first to discover that insulin therapy before GLP-1 RA therapy does not exert an additive effect on glycemic control to the GLP-1 RA first regimen in individuals with poorly controlled type 2 diabetes.

To date, meta-analyses (with study periods of 16–156 weeks)[20,21] and the clinical trials of LEAD[6], DURATION-3[7] and Exenatide versus Insulin Glargine in Patients with Suboptimally Controlled Type 2 Diabetes (GWAA)[22] have compared the safety and efficacy of GLP-1 RAs versus insulin in participants with type 2 diabetes inadequately controlled by oral hypoglycemic agents. Evidence has shown that GLP-1 RAs are equal or superior to basal insulin in reducing HbA1c levels, although no impressive differences have been observed when stratifying participants by baseline HbA1c quartiles[5–7]. Although this latter outcome might seem somewhat unexpected, the average baseline HbA1c level in the aforementioned participants was low (~8%), and thus, such studies might be insufficient to elucidate the involvement of possible GLP-1 resistance among those with higher baseline HbA1c values. In the present study, the average baseline FPG and HbA1c values were 228.9 ± 113.9 mg/dL and 10.0% ± 1.8%, respectively, which were much greater than those described in previous research[6,7,22–25]. Furthermore, when we stratified participants with baseline HbA1c levels between 7.6% and 16.5%, both therapy regimens significantly reduced the FPG and HbA1c levels by the end of the first and second phases across all HbA1c quartiles. Taken together, these findings negate the possibility of GLP-1 resistance induced by glucose toxicity, at least in humans.

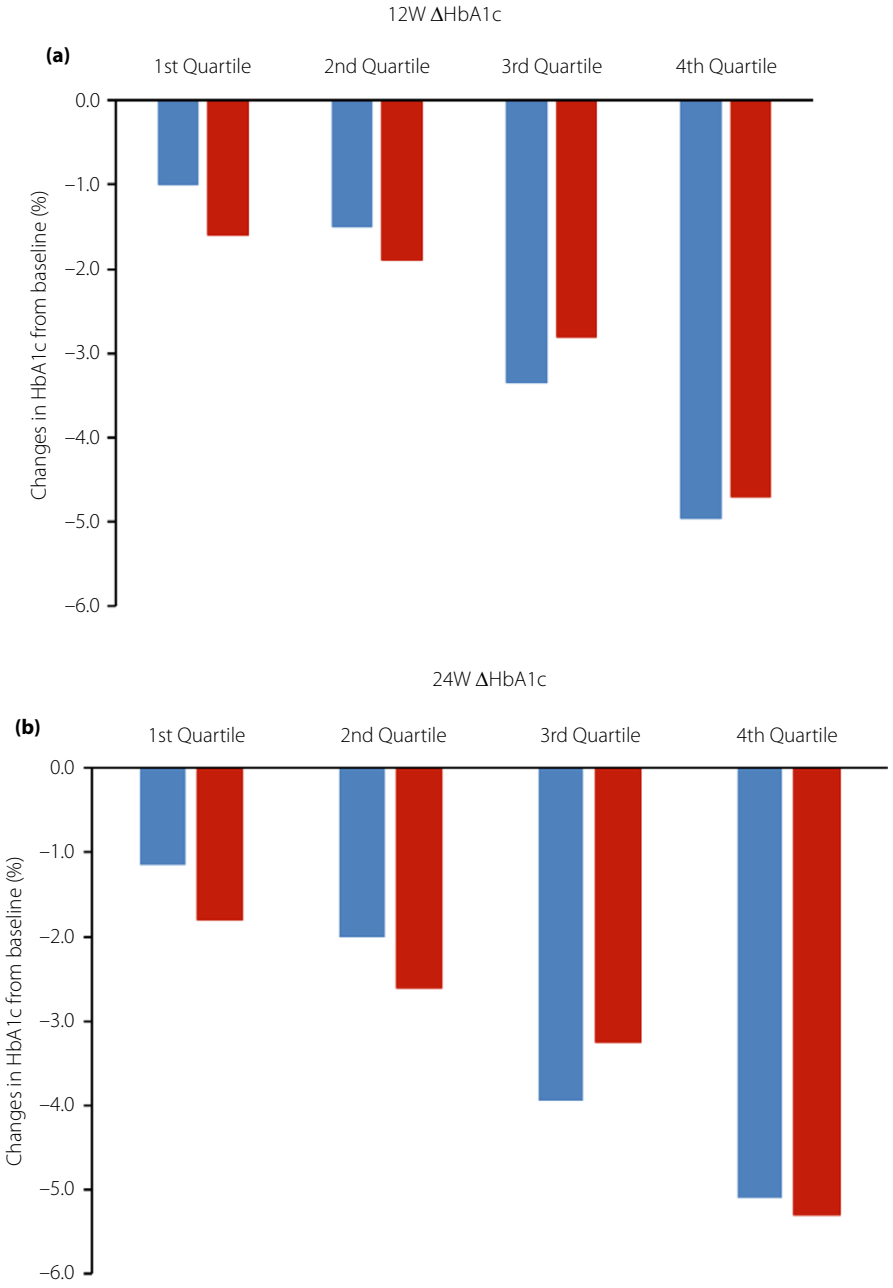

Figure 1 | Changes in glycated hemoglobin (HbA1c) levels at (a) weeks 12 and (b) 24 weeks, assessed according to the participants' baseline HbA1c quartile. Blue, glucagon-like peptide-1 receptor agonist first group; Red box; receive once-daily insulin therapy, degludec, for 12 weeks and then liraglutide for 12 weeks relay group.

We evaluated some indirect indices for insulin secretion. As shown in Tables 1 and S2, fasting C-peptide levels were elevated, whereas bodyweight was reduced similarly in both groups. These findings suggest improved insulin secretion either in the 'Insulin–GLP-1 RA relay regimen' or 'GLP-1 RA first regimen,' which might be indirect evidence for amelioration of glucose toxicity states.

In an animal study[12], hyperglycemia downregulated the GLP-1 receptor, which was restored by glucose normalization with phlorizin, in the b-cells both in the insulinopenic diabetic model (partially pancreatomized rats) and the obese diabetic model (*db*/*db* mice). Therefore, we carried out stratified subanalyses in terms of fasting level of C-peptide and BMI, as shown in Tables S5 and S6, respectively.

The Insulin–GLP-1 RA relay regimen might overcome glucose toxicity-induced GLP-1 resistance in insulinopenic type 2 diabetes participants based on the HbA1c-stratified FAS findings that the reduction of HbA1c in the Insulin–GLP-1 RA

Table 2 | Changes in glycated hemoglobin and fasting plasma glucose according to baseline glycated hemoglobin quartile

	Insulin–GLP-1 RA relay				GLP-1 RA first					
	Before	12 weeks	24 weeks	*P**	Before	12 weeks	24 weeks	*P**	*P***	*P****
HbA1c 7.6–8.7% (Q1)	*n* = 13				*n* = 14					
FPG	150.0 (127.5–177.5)	129.0 (85.0–145.5)	120.0 (106.0–143.0)	0.041	155.5 (140.3–187.0)	136.0 (100.8–153.8)	137.0 (115.0–153.3)	0.019	1.000	0.756
HbA1c	8.10 (7.75–8.30)	6.70 (5.75–7.30)	6.40 (5.45–7.35)	0.004	8.10 (7.97–8.33)	7.25 (6.40–7.85)	7.10 (6.45–7.83)	0.012	0.220	0.375
Insulin dose		10.0 (7.5–24.3)								
HbA1c 8.8–9.6% (Q2)	*n* = 15				*n* = 15					
FPG	214.0 (148.0–280.0)	135.0 (120.0–213.0)	120.0 (98.0–139.0)	0.001	163.0 (150.0–200.0)	137.0 (106.0–159.0)	136.0 (119.0–163.0)	0.010	0.067	0.005
HbA1c	9.10 (9.00–9.50)	7.10 (6.50–8.80)	6.50 (6.10–7.50)	0.001	9.20 (8.80–9.40)	7.50 (6.40–8.90)	7.50 (6.50–8.20)	0.005	0.539	0.137
Insulin dose		10.0 (8.0–18.0)								
HbA1c 9.7–10.9 (Q3)	*n* = 16				*n* = 14					
FPG	188.5 (142.8–217.3)	131.5 (102.8–179.3)	146.5 (106.8–180.5)	0.008	240.5 (166.0–282.0)	133.0 (110.3–164.3)	127.0 (111.0–163.0)	0.006	0.193	0.193
HbA1c	10.25 (9.93–10.60)	7.45 (7.03–8.35)	7.30 (6.08–8.80)	0.001	10.20 (9.88–10.83)	6.55 (6.08–9.05)	5.90 (5.78–8.83)	0.002	0.423	0.448
Insulin dose		14.0 (8.8–23.0)								
HbA1c 11.0–16.5% (Q4)	*n* = 15				*n* = 12					
FPG	348.0 (262.0–472.0)	110.0 (91.0–144.0)	131.0 (98.0–217.0)	0.001	249.0 (224.0–407.0)	124.0 (110.8–211.8)	131.5 (102.8–153.8)	0.003	0.277	0.347
HbA1c	11.70 (11.30–13.70)	7.00 (6.30–9.00)	6.40 (5.80–9.50)	0.001	12.30 (11.63–12.78)	7.10 (6.43–10.80)	6.90 (6.23–9.10)	0.005	0.867	0.683
Insulin dose		19.0 (10.5–33.0)								

All values are median (interquartile range). **P*-value for the intragroup comparison (baseline vs 24 weeks); ***P*-value for the intergroup comparison (change from baseline between groups, 12 weeks); ****P*-value for the intergroup comparison (change from baseline between groups, 24 weeks). FPG, fasting plasma glucose; GLP-1 RA first, glucagon-like peptide-1 receptor agonist first group; HbA1c, glycated hemoglobin; Insulin–GLP-1 RA, receive once-daily insulin therapy, degludec, for 12 weeks and then liraglutide for 12 weeks relay.

Table 3 | Adverse events

	Insulin–GLP-1 RA relay n = 59	GLP-1 RA first n = 57
0–12 weeks		
Nausea	0	9 (2)
Hypoglycemia	4 (1)	0
Hyperglycemia	1 (1)	0
Pneumoniae	1 (1)	0
Abdomen distension	0	2
Constipation	0	1
Appetite loss	0	1
Diarrhea	0	1
Palpitation without hypoglycemia	0	1
12–24 weeks		
Nausea	4 (1)	1
Hypoglycemia	1 (1)	0
Injection site wheal and flare	1 (1)	0
Constipation	1 (1)	1
Diarrhea	1	0
Dizziness	1	0
Appetite loss	1	0
General malaise	1	0

Number of participants who discontinued the study medication. GLP-1 RA first, glucagon-like peptide-1 receptor agonist first group; Insulin–GLP-1 RA, receive once-daily insulin therapy, degludec, for 12 weeks and then liraglutide for 12 weeks relay.

relay group tended to be bigger than that in the GLP-1 RA first group in the lowest CPR quartile. These findings are consistent with the previous observation study by Usui *et al.*[26] However, because baseline HbA1c was significantly higher in the Insulin–GLP-RA relay group in the lowest baseline CPR quartile, we should carefully conclude whether glucose toxicity-induced GLP-1 resistance exists in the insulinopenic participants. In contrast, no differences in the FPG and HbA1c across all baseline BMI quartiles were observed between the Insulin–GLP-1 RA relay group and the GLP-1 RA first groups, suggesting that BMI might not be involved in the hyperglycemia-induced GLP-1 resistance.

Dosing algorithms are important in evaluating the efficacy of insulin formulations. In the present study, the initial dosing of degludec was selected according to the doses used in clinical trials[13,14]. However, by week 12, the average daily dose was lower than that observed in predominantly Western populations[6,7,13,14,22], but similar to that reported in Japanese populations[24,25]. Furthermore, the FPG levels in our Insulin–GLP-1 RA relay group were congruent with those detected in the investigations using basal insulin[6,7,22]. In the per protocol set, the mean achieved FPG levels were 127.5 ± 47.1 mg/dL (median achieved FPG levels were 133.0 mg/dL), which seem similar to the previous studies, such as the DURATION-3 (mean achieved FPG 124.2 mg/dL) and the LEAD-5 (mean achieved FPG 131.6 mg/dL).

Interestingly, the incidence of hypoglycemia in the Insulin–GLP-1 RA relay group was lower than that of prior research aiming to improve the levels of basal insulin[6,7,13,14]. At the present study's midway point, the GLP-1 RA first group showed a significantly greater reduction in bodyweight, BMI and waist circumference compared with the Insulin–GLP-1 RA relay group (Tables S2 and S3), which is consistent with the findings from meta-analyses[20,21]. However, by 24 weeks, the changes between the groups were not appreciable, as liraglutide was found to significantly decrease the aforementioned variables in the Insulin–GLP-1 RA relay group during the study's second phase. Indeed, among Japanese participants with type 2 diabetes, it is well established that switching from insulin therapy to liraglutide decreases glycemic levels and bodyweight[18,27,28]; thus, the administration of a GLP-1 RA might be more ideal, as it prevents the development of hypoglycemia and excess adiposity.

The present study suggests some beneficial effects in the Insulin–GLP-1 RA relay regimen. First, alanine aminotransferase levels significantly decreased in the Insulin–GLP-1 RA relay group, but not in the GLP-1 RA first group. Second, peripheral endothelial function assessed by reactive hyperemia index significantly increased in the Insulin–GLP-1 RA relay group, but not in the GLP-1 RA first group. Third, creatinine and uric acid levels significantly increased in the GLP-1 RA first group, but not in the Insulin–GLP-1 RA relay group. These changes were observed under similar glycemic control and weight reduction between the groups. The possible beneficial significance of initial insulin therapy under poor glycemic status should be examined in the future.

The overall treatment satisfaction scores assessed by DTSQ significantly increased in both groups, with no significant differences between the groups. These findings might be attributable to significant improvement in glycemic control in both groups with no significant changes between the groups.

The present study had some limitations. First, this study had a relatively higher dropout rate than we had expected before the study, which might cause insufficient statistically significant differences in the analyses and difficulty in subanalyses. Second, incretin effects might be more profound in the Asian and far east populations. Hence, further large-scale clinical studies including other populations are required to confirm our conclusion. Third, a once-daily insulin regimen might be insufficient to eliminate glucose toxicity before using GLP-1 RA. However, we were afraid that multiple injections themselves become a bias to affect glycemic control compared with the once-daily GLP-1 RA regimen. Fourth, we could not calculate the achieved time to the target glucose levels in the present study. However, we already reported in a past study that the time to achieve the target glucose levels were 9.4 ± 3.2 days with once-daily basal insulin[29].

In conclusion, in poorly controlled participants with endogenous insulin secretion-preserved type 2 diabetes, insulin therapy before GLP-1 RA therapy does not exert an additive effect on glycemic control to the GLP-1 RA first regimen in individuals with poorly controlled type 2 diabetes. Hence, once-daily liraglutide is an effective alternative to once-daily insulin

degludec in glucose toxicity states, avoiding weight gain and hypoglycemia. However, in participants with insulinopenic type 2 diabetes, prior glycemic control with insulin might overcome glucose toxicity-induced GLP-1 resistance.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: the ethics committee of Kanazawa University Hospital in Japan (approval number; 2013-081 (1538), 16 April 2014).
Informed consent: Before participation, all eligible individuals provided.
Registry and the registration no. of the study/trial: This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000014140: 2 June 2014).
Animal studies: N/A.

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REFERENCES

1. Kristensen SL, Rørth R, Jhund PS, *et al*. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; 7: 776–785.
2. Herrera Comoglio R, Vidal GX. Cardiovascular outcomes, heart failure and mortality in type 2 diabetic patients treated with glucagon-like peptide 1 receptor agonists (GLP-1 RAs): a systematic review and meta-analysis of observational cohort studies. *Int J Clin Pract* 2020; 74: e13553.
3. Association AD. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2020. *Diabetes Care* 2020; 43: S98–110.
4. Haneda M, Noda M, Origasa H, *et al*. Japanese clinical practice guideline for diabetes 2016. *Diabetol Int* 2018; 9: 1–45.
5. Buse JB, Peters A, Russell-Jones D, *et al*. Is insulin the most effective injectable antihyperglycaemic therapy? *Diabetes Obes Metab* 2015; 17: 145–151.
6. Russell-Jones D, Vaag A, Schmitz O, *et al*. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 2009; 52: 2046–2055.
7. Diamant M, Van Gaal L, Stranks S, *et al*. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010; 375: 2234–2243.
8. Kjems LL, Holst JJ, Volund A, *et al*. The influence of GLP-1 on glucose-stimulated insulin secretion: effects on -cell sensitivity in type 2 and nondiabetic subjects. *Diabetes* 2003; 52: 380–386.
9. Højberg PV, Vilsbøll T, Rabøl R, *et al*. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia* 2009; 52: 199–207.
10. Arakawa M, Ebato C. Efficacy of liraglutide as a follow-up therapy after resolution of glucotoxicity with intensive insulin therapy. *Diabetes Metab Syndr* 2013; 7: 223–225.
11. Vilsbøll T, Krarup T, Madsbad S, *et al*. Defective amplification of the late phase insulin response to glucose by GIP in obese type II diabetic patients. *Diabetologia* 2002; 45: 1111–1119.
12. Xu G, Kaneto H, Laybutt DR, *et al*. Downregulation of GLP-1 and GIP receptor expression by hyperglycemia: possible contribution to impaired incretin effects in diabetes. *Diabetes* 2007; 56: 1551–1558.
13. Holman RR, Farmer AJ, Davies MJ, *et al*. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361: 1736–1747.
14. Bretzel RG, Nuber U, Landgraf W, *et al*. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. *Lancet* 2008r; 371: 1073–1084.
15. Araki E, Goto A, Kondo T, *et al*. Japanese clinical practice guideline for diabetes 2019. *Diabetol Int* 2020; 11: 165–223.
16. Moerland M, Kales AJ, Schrier L, *et al*. Evaluation of the EndoPAT as a tool to assess endothelial function. *Int J Vasc Med* 2012; 20: 904141.

17. Bradley C, Plowright R, Stewart J, *et al*. The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. *Health Qual Life Outcomes* 2007; 5: 57.
18. Nambu T, Matsuda Y, Matsuo K, *et al*. Liraglutide administration in type 2 diabetic patients who either received no previous treatment or were treated with an oral hypoglycemic agent showed greater efficacy than that in patients switching from insulin. *J Diabetes Investig* 2013; 4: 69–77.
19. Osonoi T, Onishi Y, Nishida T, *et al*. Insulin degludec versus insulin glargine, both once daily as add-on to existing orally administered antidiabetic drugs in insulin-naive Japanese patients with uncontrolled type 2 diabetes: subgroup analysis of a pan-Asian, treat-to-target phase 3 trial. *Diabetol Int* 2016; 7: 141–147.
20. Abd El Aziz MS, Kahle M, Meier JJ, *et al*. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes Metab* 2017; 19: 216–227.
21. Singh S, Wright EE, Kwan AYM, *et al*. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab* 2017; 19: 228–238.
22. Heine RJ, Van Gaal LF, Johns D, *et al*. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; 143: 559–569.
23. Araki E, Inagaki N, Tanizawa Y, *et al*. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. *Diabetes Obes Metab* 2015; 17: 994–1002.
24. Inagaki N, Atsumi Y, Oura T, *et al*. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferio. *Clin Ther* 2012; 34: 1892–1908.
25. Miyagi M, Uchino H, Kumashiro N, *et al*. Up-titration strategy after DPP-4 inhibitor-based oral therapy for type 2 diabetes: a randomized controlled trial shifting to a single-dose GLP-1 enhancer versus adding a variable basal insulin algorithm. *Diabetes Ther* 2018; 9: 1959–1968.
26. Usui R, Sakuramachi Y, Seino Y, *et al*. Retrospective analysis of liraglutide and basal insulin combination therapy in Japanese type 2 diabetes patients: the association between remaining β-cell function and the achievement of the glycated hemoglobin target 1 year after initiation. *J Diabetes Investig* 2018; 9: 822–830.
27. Rose TN, Jacobs ML, Reid DJ, *et al*. Real-world impact on monthly glucose-lowering medication cost, HbA1c, weight, and polytherapy after initiating a GLP-1 receptor agonist. *J Am Pharm Assoc* 2003; 60: 31–38.
28. Iida N, Mizukoshi E, Yamashita T, *et al*. Overuse of antianaerobic drug is associated with poor postchemotherapy prognosis of patients with hepatocellular carcinoma. *Int J Cancer* 2019; 145: 2701–2711.
29. Takeshita Y, Tanaka T, Wakakuri H, *et al*. Metabolic and sympathovagal effects of bolus insulin glulisine versus basal insulin glargine therapy in people with type 2 diabetes: a randomized controlled study. *J Diabetes Investig* 2021; 12: 1193–1201.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Baseline characteristics of the study participants.

Table S2 | Changes in the participants' characteristics between baseline and 24 weeks (per protocol set).

Table S3 | Changes in the participants' characteristics between baseline and 12 weeks (full analysis set).

Table S4 | Changes in the treatment satisfaction scores.

Table S5 | Changes in glycated hemoglobin and fasting plasma glucose according to baseline CPR quartile.

Table S6 | Changes in glycated hemoglobin and fasting plasma glucose according to baseline body mass index quartile.

Table S7 | Changes in the participants' characteristics between baseline and 24 weeks with and without antidiabetes medications.

Figure S1 | Study protocol.

Figure S2 | Flowchart of the study participants.