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ORIGINAL RESEARCH

The Effect of Linagliptin versus Metformin Treatment-Related Quality of Life in Patients with Type 2 Diabetes Mellitus

Tomoya Mita · Toru Hiyoshi · Hidenori Yoshii · Hiroko Chimori · Kazuo Ikeda · Miho Shimizu · Yuichi Kojima · Hareaki Yamamto · Daijiro Yasuda · Junko Sato · Hirotaka Watada

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ABSTRACT

Introduction: There have been no studies directly comparing the effect of dipeptidyl peptidase-4 inhibitors with that of metformin on treatment-related quality of life (QOL) when used as first-line therapy in patients with type 2 diabetes mellitus (T2DM).

Methods: This study is a prospective, randomized, open-label, multicenter, parallel-group, comparative study. Forty-four participants who failed to achieve target glycemic control with diet and exercise therapy were randomly allocated to receive linagliptin or metformin therapy. We compared treatment-related QOL among the two groups using the Oral Hypoglycemic Agent Questionnaire, version 2 (OHA-Q version 2) and the self-administered Diabetes Therapy-Related QOL (DTR-QOL) questionnaire.

Results: After randomization, 21 patients in the linagliptin group and 22 patients in the metformin treatment group were included in the full analysis set. Biochemical parameters,

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T. Mita (✉) · H. Watada
Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan
e-mail: tom-m@juntendo.ac.jp

T. Hiyoshi
Division of Diabetes and Endocrinology, Japanese Red Cross Medical Center, Shibuya-ku, Tokyo, Japan

H. Yoshii
Department of Medicine, Diabetology and Endocrinology, Juntendo Tokyo Koto Geriatric Medical Center, Koto-ku, Tokyo, Japan

H. Chimori
Chimori Medical Clinic, Fukushima-ku, Osaka, Osaka, Japan

K. Ikeda
Ikeda Shinryojyo, Higashiosaka, Osaka, Japan

M. Shimizu
Shimizu Clinic, Higashi Yodogawa-ku, Osaka, Osaka, Japan

Y. Kojima
Musashino Family Clinic, Yoshikawa, Saitama, Japan

H. Yamamto
Yamamoto Clinic, Sagamihara, Kanagawa, Japan

D. Yasuda
Yasuda Clinic, Ota-ku, Tokyo, Tokyo, Japan

J. Sato
Department of Diabetes, Endocrinology and Metabolism, Juntendo University Shizuoka Hospital, Izunokuni, Shizuoka, Japan

incidence of adverse effects, and rate of adherence to medication were comparable between the two groups. Over the 24-week treatment period, no significant differences in overall OHA-Q scores between the groups were observed, although the subscale 1 (treatment convenience) score was significantly higher in the linagliptin group than in the metformin group. The overall DTR-QOL score did not differ between the two groups; however, the DTR-QOL scores significantly improved after 24 weeks of linagliptin treatment, but not after metformin treatment.

Conclusion: We did not find significantly better treatment-related QOL with linagliptin among Japanese patients with T2DM. In terms of treatment convenience, our data showed that linagliptin was superior to metformin.

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Keywords: Linagliptin; Metformin; Questionnaire; Treatment-related quality of life; Type 2 diabetes mellitus

INTRODUCTION

One of the main objectives of diabetes management is to maintain quality of life (QOL) [1]. It has been reported that advanced age, poor glycemic control, previous hypoglycemic episodes, and complex therapeutic regimens are associated with lower QOL in patients with type 2 diabetes mellitus (T2DM) [2–5]. Given that a lower treatment-related QOL is associated with reduced patient motivation and adherence with treatment among patients with T2DM [6], it is important that treatment-related QOL be taken into consideration in the choice of oral antihypoglycemic agents (OHAs).

Treatment guidelines by the American Diabetes Association and European Association for the Study of Diabetes recommend metformin as first-line therapy when lifestyle modification alone fails to achieve or maintain optimal glycemic goals [7]. Metformin is effective in lowering blood glucose levels by improving insulin sensitivity without increasing the risk of hypoglycemia. Metformin is also associated with weight neutrality or loss, and is generally safe, well tolerated, and inexpensive [8]. In addition, metformin might also reduce the incidence of cardiovascular events [9]. However, a recent meta-analysis demonstrated that adherence to metformin was worse than that for other OHAs such as sulfonylureas and thiazolidinediones [10]. The adverse effects associated with metformin therapy (e.g., gastrointestinal side effects) and the dosing frequency of this agent may negatively affect patient adherence to therapy.

Conversely, the Japan Diabetes Society treatment guidelines recommend choosing suitable therapies in line with the dominant pathophysiological condition in each patient, such as insufficient insulin secretion or insulin resistance [11], because T2DM in East Asians is more strongly associated with beta-cell dysfunction than with insulin resistance or adiposity [12]. In this context, various types of OHAs, including metformin and dipeptidyl peptidase (DPP)-4 inhibitors, are often chosen as first-line therapy in Japan [13].

DPP-4 inhibitors, such as linagliptin, enhance glucose-dependent insulin secretion from pancreatic beta cells via inhibition of the degradation of active incretins by DPP-4. In general, DPP-4 inhibitors are safe and well tolerated and do not cause weight gain [14]. More specifically, three recent randomized clinical studies showed that the use of DPP-4 inhibitors did not increase or decrease the cardiovascular event rate in T2DM patients compared to placebo [15–17]. A retrospective cohort study and meta-analysis demonstrated that DPP-4 inhibitors also did not increase the risk of cardiovascular disease compared to sulfonylurea [18, 19]. An additional advantage of linagliptin is that dose adjustment is not necessary in patients with end-stage renal disease because this DPP-4 inhibitor is mainly excreted in the feces. Consequently, it is relatively widely used in this patient population and has similar glucose-lowering effect as other DPP-4 inhibitors even in those patients [20]. Due to those characteristics, DPP-4 inhibitors, including linagliptin,

are now the most frequently prescribed first-line agents for T2DM in Japan [21].

In this study, we evaluated the effect of linagliptin versus metformin on treatment-related QOL in patients with T2DM using the Oral Hypoglycemic Agent Questionnaire, version 2 (OHA-Q version 2) [22] and the self-administered Diabetes Therapy-Related QOL (DTR-QOL) questionnaire [23].

METHODS

Study Design

The INitial choice of DPP-4 inhibitor in Japanese T2DM patients: Effect of Linagliptin on QOL (INTEL-QOL) study is a prospective, randomized, open-label, multicenter, parallel-group, comparative trial that has been described previously [24]. This study is registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors (ICMJE) (UMIN000022953).

Study Population

Japanese patients with T2DM who regularly attended the outpatient diabetes clinics of 14 medical institutions in Japan (Chimori Clinic, Ikeda Clinic, Yamamoto Clinic, Japanese Red Cross Medical Center, Juntendo Tokyo Koto Geriatric Medical Center [Department of Medicine, Diabetology, and Endocrinology], Juntendo University Graduate School of Medicine [Department of Metabolism & Endocrinology], Juntendo University Shizuoka Hospital [Department of Diabetes, Endocrinology, and Metabolism], Sawaki Internal Medicine and Diabetes Clinic, Shimizu Clinic, Tanaka Clinic, Menju Clinic, Misaki Naika Clinic, Musashino Family Clinic, and Yasuda Clinic) were asked to participate in this study. The inclusion criteria were: (1) T2DM not at target blood glucose control as specified in the Treatment Guide for Diabetes by the Japan Diabetes Society [25], despite the introduction of diet and/or exercise therapy; (2) initiation of OHAs in addition to diet and/or exercise therapy; (3) age $\geq$ 20 years and $<$ 75 years, regardless of gender; and (4) written informed consent for study participation. The exclusion criteria were: (1) type 1 or secondary diabetes; (2) acute complications of diabetes within the past 6 months; (3) congestive heart failure or myocardial infarction requiring pharmacotherapy; (4) unstable angina pectoris or coronary bypass surgery within the past 6 months; (5) chronic cirrhosis or chronic active hepatitis; (6) artificial dialysis or moderate renal dysfunction; (7) aspartate aminotransferase or alanine aminotransferase levels more than threefold the upper limit of the normal range; (8) direct bilirubin more than threefold the upper limit of the normal range, clinically abnormal thyroid-stimulating hormone level, or fasting triglyceride levels of $>$ 7.9 mmol/L; (9) treatment with any type of antidiabetic medication; (10) dementia, possible dementia, or mental disorder; (11) insufficient capacity for judgment or illiteracy; (12) requiring consent for study participation from a legal representative; (13) pregnancy, lactation, possibly pregnancy, or planning to become pregnant during the study period; (14) history of hypersensitivity to the investigational drugs; (15) present or past history of cancer, unless there was no current medical therapy, no recurrence to date, and no risk of recurrence during this study; and (16) judged as ineligible by the clinical investigators.

Consecutive subjects were screened. Patients that met the above eligibility criteria were asked to participate in the present study. All patients who agreed to participate were enrolled in the study. The protocol was approved by the institutional review board of each participating institution. The study protocol is in compliance with the Declaration of Helsinki and current legal regulations in Japan. All procedures are in accordance with the ethical standards of the institutional and national committees responsible for human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients before being included in the study.

Randomization and Study Intervention

Patients were registered at the INTEL-QOL trial's administration office via the internet. Once enrolled, patients were randomly assigned to either the linagliptin or metformin group. Randomization was performed using a dynamic allocation method based on age (< 65 or ≥ 65 years) and gender.

Patients in the linagliptin group were started on linagliptin 5 mg once daily. Patients in the metformin group were started on metformin 250 mg twice daily. The study protocol encouraged increasing the dose of metformin to a maximum dose of 2250 mg when the glycated hemoglobin (HbA1c) level was ≥ 7.0% [25]. In both groups, the addition of OHAs other than the study drugs and insulin were not permitted during the study.

Study Variables and Study Schedule

The study variables and study schedule are shown in Table 1 and Electronic Supplementary Material (ESM) Fig. 1. The study period consisted of 24 weeks after registration. The registration period was from June 2016 to December 2017. The full study duration was from June 2016 to September 2018. All randomized participants were followed until the end of the scheduled study, regardless of adherence to or discontinuation of the study medication for any reason. The investigators were encouraged to provide standard medical care during the study. As a general rule, participants were asked to make routine visits to the clinic every 4–8 weeks during study. During this visit, clinical outcomes, adherence, and adverse events were ascertained. Clinical and biochemical data were collected at baseline and 24 weeks after randomization. Blood samples were obtained after overnight fasting. Urinary albumin excretion was measured using a latex agglutination assay on a spot urine sample at baseline and 24 weeks after randomization. Participants were also asked to record their usage of the study drug on a medication record during the study period.

Study Outcomes

The primary study outcome was the difference in the overall OHA-Q version 2 score between the two treatment groups at the end of the study. The secondary outcomes were: (1) the difference in score for each OHA-Q version 2 subscale between the two treatment groups at the end of the study; (2) change in overall DTR-QOL score and score for each DTR-QOL domain from baseline to 24 weeks; (3) change in HbA1c level from baseline to 24 weeks; (4) change in all other measured parameters, as reported by Mita et al. [24]. Hypoglycemia was defined based on confirmation of a sign and symptoms of hypoglycemia without a capillary blood glucose measurement.

OHA-Q Version 2

The OHA-Q version 2 is a 23-item, self-administered assessment with three subscales: subscale 1, treatment convenience (9 items; questions 1–9); subscale 2, somatic symptoms (11 items; questions 11–21); and subscale 3, satisfaction (3 items; questions 10, 22, and 23) (ESM Table 1) [22]. The response to each question is scored using a Likert-type scale that ranges from 1 to 4 points. Answers are converted to scores of 0 to 3. Subscale scores are calculated by summing the response to the items in each subscale. If there were missing values for any item in a subscale, the score of that subscale and the overall OHA-Q score are calculated as previously described [22]. Higher scores represent higher QOL. We used the original Japanese version of the OHA-Q version 2.

DTR-QOL Questionnaire

The DTR-QOL questionnaire is a 29-item, self-administered assessment with four primary scales: domain 1, burden on social activities and daily activities (13 items); domain 2, anxiety and dissatisfaction with treatment (8 items); domain 3, hypoglycemia (4 items); domain 4, satisfaction with treatment (4 items) (ESM Table 1) [23]. The DTR-QOL questionnaire can be used to evaluate the effect of diabetes

Table 1 Clinical characteristics of patients by treatment group

Parameters	Linagliptin group (n = 21)	Metformin group (n = 22)	P value
Age (years)	61.3 ± 8.7	58.1 ± 13.8	0.37
Gender (male) (%)	13 (62)	13 (59)	1.00
Estimated duration of diabetes (years)[a]	3.4 ± 5.9	3.3 ± 4.1	0.95
Current smoker (yes)	4 (20)	5 (23)	1.00
Anti-hypertensive drugs			
Angiotensin-converting enzyme inhibitors	0 (0)	1 (4.5)	1.00
Angiotensin II receptor blockers	5 (24)	7 (32)	0.74
Direct renin inhibitors	0 (0)	0 (0)	–
Calcium channel blockers	4 (19)	6 (27)	0.72
Diuretics	0 (0)	0 (0)	–
α-Adrenergic receptor antagonists	0 (0)	0 (0)	–
β-Adrenergic receptor antagonists	4 (19)	2 (9)	0.41
Lipid-lowering agents			
Statins	4 (19)	7 (32)	0.49
Ezetimibe	0 (0)	0 (0)	–
Fibrates	0 (0)	1 (4.5)	1.00

Data are presented as the number of patients with the percentage (%) in parenthesis or as the mean ± standard deviation (SD)

[a] Data were available for 17 patients in the linagliptin group and 18 patients in the metformin group

treatment on patient QOL with high reliability and validity [23]. The response to each question is scored using a Likert-type scale that ranges from 1 (strongly agree) to 7 (strongly disagree). The scale for items 26–29 is reversed, so that 7 represent the highest QOL score. Domain scores are calculated by summing the response to the items in each domain. If there are missing values for any item in a domain, they are handled as described in the original report [23]. Scores are then converted to a range of 0–100. Higher scores represent higher QOL. In each domain, average scores are calculated. We used the original Japanese version of the DTR-QOL.

Sample Size

The sample size was not calculated using scientific methods because this was an exploratory study. Assuming a treatment dropout rate of 10%, the target number of enrolled patients was set at 22 subjects in each group, or 44 subjects in total.

Statistical Analysis

The results are presented as the mean ± standard deviation or as the median with the interquartile range for continuous variables, and as a number with the proportion (percentage) of patients for categorical variables. Efficacy was analyzed using the full analysis set. To compare the overall OHA-Q version 2 score and each OHA-Q version 2 subscale score between the two treatment groups at the end of the study, we used Student's t test and analysis of covariance models (ANCOVA) that included treatment group as a fixed effect and the

allocation factors of age (< 65 or ≥ 65 years) and gender as covariates . To compare the changes in total and domain-specific DTR-QOL scores, HbA1c, and fasting blood glucose between the two treatment groups at the end of the study, we used Student's *t* test and ANCOVA models that included treatment group as a fixed effect and (1) each baseline value as a covariate, (2) allocation factors as covariates, and (3) each baseline value and allocation factors as covariates. For other variables, comparisons between the groups were performed using Student's *t* test or the Wilcoxon rank-sum test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. Changes from baseline to week 24 within each treatment group were assessed with the one-sample Student's *t* test or Wilcoxon signed-rank test. The correlation between the overall OHA-Q version 2 score at the end of study or change in the DTR-QOL score from baseline to 24 weeks, and parameters such as (1) age, gender, body mass index (BMI), duration of diabetes, HbA1c, and estimated glomerular filtration rate (eGFR) at baseline, (2) change in BMI and change in HbA1c, and (3) adherence rate and dosing frequency, were evaluated using Pearson's and Spearman's correlation coefficients. All statistical tests were two-sided with a significance level of 5%. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Participants

A total of 44 participants were randomly allocated to either the linagliptin group (n = 21) or the metformin group (n = 23). After excluding one patient in the metformin group from the analysis because no data were available due to transfer of care, 21 patients in the linagliptin group and 22 patients in the metformin treatment group were included in the full analysis set (ESM Fig. 1). The two groups were well balanced at baseline, with comparable mean age, sex, BMI, estimated duration of diabetes, HbA1c level, blood pressure, biochemical parameters, and background treatment for hypertension, hyperlipidemia, and other conditions, with the exception of eGFR (Tables 1, 2).

Patients in the linagliptin group were started on linagliptin 5 mg once daily. No dose change occurred during the study. Patients in the metformin group were started on metformin 250 mg twice daily. Although investigators were encouraged to increase the dose of metformin to a maximum dose of 2250 mg when the HbA1c level was ≥ 7.0%, the dose was increased in only five patients. The dose was increased from 500 to 750 mg in one patient, and from 500 to 1000 mg in four patients. The dose was decreased from 500 to 250 mg in one patient. The mean metformin dose was 500 ± 0.0 mg/day at baseline and 568.2 ± 246.2 mg/day at week 24. In one patient in the metformin group, a sodium-glucose co-transporter-2 inhibitor was added at the investigator's discretion.

The two groups had a similar mean change in BMI at 24 weeks (Table 2). HbA1c levels and fasting serum glucose levels were significantly lower at 24 weeks than at baseline in both groups (Table 2). However, the change in HbA1c and fasting serum blood glucose levels did not differ between the two groups (Table 2). In addition, there were no significant differences in other biochemical parameters between the two groups at the end of the study, with the exception of urinary albumin excretion (Table 2).

Over the 24-week treatment period, none of the patients experienced hypoglycemia. There were no intergroup differences in the incidence of adverse effects, including gastrointestinal symptoms (one patient in the linagliptin group vs. three patients in the metformin group) and serious adverse events (linagliptin group: subarachnoid hemorrhage (n = 1), recurrence of liver cancer (n = 1), effort angina (n = 1); metformin group: none). Although recent studies suggest that DPP-4 inhibitors are associated with increased risk for acute pancreatitis [26, 27], patients on linagliptin did not experience acute pancreatitis in this short-term study. There was no significant difference in the rate of adherence to medication between the two groups (100% [97.5–100%] in the linagliptin

Table 2 Effects of linagliptin and metformin on body mass index, glucose metabolism, lipid metabolism, and blood pressure

Parameters	Linagliptin group	Metformin group	*P* value (between groups)
BMI at baseline	25.7 ± 4.5 (n = 21)	26.3 ± 4.9 (n = 22)	0.72
BMI at 24 weeks	25.7 ± 4.3 (n = 20)	26.5 ± 4.3 (n = 18)	0.56
Change in BMI from baseline to week 24	− 0.3 ± 1.4 (n = 20)	− 0.3 ± 1.2 (n = 18)	0.90
HbA1c at baseline (%)	7.1 ± 0.7 (n = 21)	7.5 ± 1.5 (n = 21)	0.28
HbA1c at 24 weeks (%)	6.6 ± 0.5 (n = 21)	7.1 ± 1.1 (n = 20)	0.06
Change in HbA1c from baseline to week 24	− 0.5 ± 0.4[a] (n = 21)	− 0.5 ± 0.9[a] (n = 19)	0.78
Fasting blood glucose at baseline (mmol/L)	8.1 ± 2.6 (n = 18)	9.0 ± 3.8 (n = 19)	0.41
Fasting blood glucose at 24 weeks (mmol/L)	7.2 ± 1.3 (n = 19)	7.6 ± 1.2 (n = 20)	0.34
Change in fasting blood glucose from baseline to week 24	− 1.0 ± 1.6[a] (n = 18)	− 1.8 ± 3.9 (n = 19)	0.42
Total cholesterol at baseline (mmol/L)	5.3 ± 1.0 (n = 20)	5.3 ± 0.9 (n = 19)	0.91
Total cholesterol at baseline (mmol/L)	4.8 ± 1.0 (n = 20)	5.2 ± 0.8 (n = 19)	0.26
Change in total cholesterol from baseline to week 24	− 0.5 ± 1.1 (n = 19)	− 0.2 ± 0.7 (n = 19)	0.35
LDL cholesterol at baseline (mmol/L)	3.2 ± 1.0 (n = 16)	3.1 ± 0.7 (n = 16)	0.70
LDL cholesterol at 24 weeks (mmol/L)	2.8 ± 0.8 (n = 19)	3.0 ± 0.8 (n = 18)	0.50
Change in LDL cholesterol from baseline to week 24	− 0.1 ± 1.0 (n = 15)	− 0.2 ± 0.7 (n = 14)	0.77
HDL cholesterol at baseline (mmol/L)	1.4 ± 0.4 (n = 20)	1.4 ± 0.3 (n = 22)	0.61
HDL cholesterol at 24 weeks (mmol/L)	1.3 ± 0.4 (n = 21)	1.4 ± 0.2 (n = 20)	0.48
Change in HDL cholesterol from baseline to week 24	0.0 ± 0.2 (n = 20)	0.0 ± 0.3 (n = 20)	0.76
Triglycerides at baseline (mmol/L)	1.7 ± 0.9 (n = 18)	2.0 ± 1.3 (n = 19)	0.33
Triglycerides at 24 weeks (mmol/L)	1.4 ± 0.5 (n = 19)	1.8 ± 1.1 (n = 20)	0.11
Change in triglycerides from baseline to week 24	− 0.3 ± 0.6 (n = 17)	− 0.3 ± 1.2 (n = 17)	0.99
AST at baseline (IU/L)	26.6 ± 10.8 (n = 21)	30.5 ± 22.1 (n = 22)	0.47
AST at 24 weeks (IU/L)	25.0 ± 10.6 (n = 21)	28.1 ± 16.5 (n = 20)	0.49
Change in AST from baseline to week 24	− 1.5 ± 6.3 (n = 21)	− 4.1 ± 10.6 (n = 20)	0.35
ALT at baseline (IU/L)	26.9 ± 16.7 (n = 21)	37.1 ± 32.1 (n = 22)	0.20
ALT at 24 weeks (IU/L)	21.3 ± 10.4 (n = 21)	33.3 ± 24.0 (n = 20)	0.06
Change in ALT from baseline to week 24	− 4.5 ± 8.9[a] (n = 21)	− 6.5 ± 19.4 (n = 20)	0.67
eGFR at baseline (mL/min/1.73 m^2)	76.7 ± 17.2 (n = 21)	92.0 ± 21.4 (n = 22)	0.014
eGFR at baseline at 24 weeks (mL/min/1.73 m^2)	76.5 ± 11.9(n = 21)	90.7 ± 19.8 (n = 20)	0.008
Change in eGFR from baseline to week 24	− 0.2 ± 14.1[a] (n = 21)	− 3.7 ± 12.0 (n = 20)	0.41

Table 2 continued

Parameters	Linagliptin group	Metformin group	*P* value (between groups)
Urinary albumin excretion at baseline (mg/g creatinine)	15.7 (5.0, 43.2) (n = 10)	20.0 (5.0, 33.4) (n = 15)	0.91
Urinary albumin excretion at 24 weeks (mg/g creatinine)	7.0 (3.3, 10.0) (n = 13)	22.5 (5.0, 39.8) (n = 14)	0.049
Change in urinary albumin excretion from baseline to week 24	− 8.0 (− 15.6, 0.3) (n = 9)	− 0.7 (− 6.7, 8.0) (n = 12)	0.20
Systolic BP at baseline (mmHg)	136 ± 16 (n = 21)	138 ± 14 (n = 22)	0.69
Systolic BP at 24 weeks (mmHg)	131 ± 16 (n = 21)	129 ± 7 (n = 20)	0.69
Change in systolic BP from baseline to week 24	− 4.8 ± 14.4 (n = 21)	− 8.9 ± 15.4[a] (n = 20)	0.38
Diastolic BP at baseline (mmHg)	80 ± 14 (n = 21)	79 ± 13 (n = 22)	0.83
Diastolic BP at 24 weeks (mmHg)	79 ± 13 (n = 21)	78 ± 7 (n = 19)	0.72
Change in diastolic from baseline to week 24	− 1.1 ± 7.9 (n = 21)	− 3.2 ± 12.5[a] (n = 19)	0.53

Data are presented as the mean ± SD or as the median with the interquartile range (IQR) in parenthesis
Differences between groups at baseline were analyzed using Student's t test or the Wilcoxon rank-sum test. Intragroup differences in the change from baseline to 24 weeks were analyzed using a one-sample t test or the Wilcoxon signed-rank test. Intergroup differences in the change from baseline to 24 weeks were analyzed using Student's t test or the Wilcoxon rank-sum test
BMI Body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, AST Aspartate transaminase, ALT alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *BP* blood pressure
[a] $P < 0.05$

group vs. 97.3% [92.8–100.0%] in the metformin group; $P = 0.08$].

OHA-Q Score and Change in DTR-QOL Scores

At 24 weeks, the two groups had comparable overall OHA-Q scores (Table 3). An ANCOVA model that included treatment group as a fixed effect and the allocation factors of age (< 65 or ≥ 65 years) and gender as covariates produced similar findings.

With respect to subscale scores, the subscale 1 "treatment convenience" score was significantly higher in the linagliptin group than in the metformin group (Table 3). Similar findings were noted in an ANCOVA model that included treatment group as a fixed effect and the allocation factors of age (< 65 or ≥ 65 years) and gender as covariates (mean change 5.35; 95% confidence interval 2.20–8.50; $P = 0.001$). In contrast, there were no differences in subscale 2 (somatic symptoms) and subscale 3 (satisfaction) scores between the two groups (Table 3). At the question level, scores for questions 1, 2, and 6–9 were significantly higher after 24 weeks of linagliptin treatment (Table 3).

Regarding the DTR-QOL questionnaire, changes in the overall DTR-QOL score and domain-specific scores over 24 weeks were similar in the two groups (Table 4). However, the change in the score for question 22 ("I am worried that complications might get worse with my current diabetes treatment") was significantly higher in the linagliptin group than in the metformin group (Table 4).

The overall DTR-QOL scores and scores for domains 1, 2, and 4 significantly improved after 24 weeks of linagliptin treatment, but not after metformin treatment. At the question level, scores for questions 10–14, 17–20, 22, 23, 26, 27, and 29 also significantly improved after

Table 3 Effects of linagliptin and metformin on the Oral Hypoglycemic Agent Questionnaire version 2 score

Parameter	Linagliptin group (n = 21)	Metformin group (n = 20)	P value (between groups)
Total score	55.0 (48.0, 58.0)	46.0 (39.5, 56.5)	0.09
Subscale 1 score	26.0 (22.0, 27.0)	18.5 (15.5, 24.5)	0.003
Subscale 2 score	23.0 (20.0, 27.0)	22.5 (19.0, 27.0)	0.70
Subscale 3 score	6.0 (5.0, 7.0)	6.0 (5.0, 6.5)	0.83
Question 1	2.0 (2.0, 3.0)	2.0 (1.0, 2.5)	0.022
Question 2	3.0 (3.0, 3.0)	2.5 (2.0, 3.0)	0.024
Question 3	3.0 (2.0, 3.0)	2.0 (1.5, 3.0)	0.05
Question 4	3.0 (3.0, 3.0)	3.0 (2.0, 3.0)	0.08
Question 5	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.51
Question 6	3.0 (2.0, 3.0)	2.0 (1.0, 2.0)	<0.001
Question 7	3.0 (2.0, 3.0)	2.0 (1.0, 2.5)	0.008
Question 8	3.0 (3.0, 3.0)	2.0 (1.0, 3.0)	0.001
Question 9	3.0 (3.0, 3.0)	2.0 (2.0, 3.0)	0.002
Question 10	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	0.97
Question 11	2.0 (2.0, 3.0)	2.0 (1.0, 2.0)	0.11
Question 12	2.0 (2.0, 3.0)	2.0 (1.5, 2.0)	0.09
Question 13	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.87
Question 14	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)	0.50
Question 15	2.0 (1.0, 2.0)	2.0 (2.0, 2.0)	0.83
Question 16	2.0 (2.0, 3.0)	2.0 (1.5, 3.0)	0.86
Question 17	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.92
Question 18	2.0 (2.0, 3.0)	2.0 (1.5, 2.0)	0.13
Question 19	2.0 (1.0, 2.0)	2.0 (1.0, 2.5)	0.50
Question 20	2.0 (1.0, 3.0)	2.0 (1.5, 2.0)	0.99
Question 21	3.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.45
Question 22	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	0.78
Question 23	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	0.99

Data are presented as the median with the IQR in parenthesis
Differences between groups at 24 weeks were analyzed using the Wilcoxon rank-sum test

24 weeks of linagliptin treatment (data not shown). For participants on metformin treatment, only the score for question 29 significantly improved after 24 weeks of treatment (data not shown).

We investigated the correlation between either OHA-Q score or change in DTR-QOL score and some parameters, at baseline and the change over 24 weeks. Medication adherence rate was the only parameter significantly

Table 4 Effects of linagliptin and metformin on the self-administered Diabetes Therapy-Related Quality of Life questionnaire score

Parameters	Linagliptin group	Metformin group	*P* value (between groups)
Total score at baseline	65.5 (43.7, 76.4) (n = 21)	64.9 (52.9, 82.5) (n = 20)	0.62
Total score at 24 weeks	80.5 (67.8, 92.0) (n = 21)	77.9 (53.7, 89.9) (n = 20)	0.45
Change in total score from baseline to week 24	9.8 (2.3, 21.8)[a] (n = 21)	10.9 (1.1, 21.3) (n = 18)	0.75
Domain 1 score at baseline	73.1 (46.2, 84.6) (n = 21)	68.6 (46.2, 91.0) (n = 22)	0.72
Domain 1 score at 24 weeks	87.2 (64.1, 96.2) (n = 21)	85.3 (55.8, 93.6) (n = 20)	0.49
Change in domain 1 score from baseline to week 24	7.7 (0.0, 16.7)[a] (n = 21)	3.2 (− 2.6, 26.3) (n = 20)	0.75
Domain 2 score at baseline	56.3 (43.8, 75.0) (n = 21)	66.7 (50.0, 79.2) (n = 22)	0.47
Domain 2 score at 24 weeks	79.2 (58.3, 91.7) (n = 21)	64.6 (43.8, 93.8) (n = 20)	0.47
Change in domain 2 score from baseline to week 24	16.7 (0.0, 33.3)[a] (n = 21)	8.3 (− 1.0, 20.8) (n = 20)	0.19
Domain 3 score at baseline	95.8 (50.0, 100.0) (n = 21)	75.8 (50.0, 100.0) (n = 22)	0.70
Domain 3 score at 24 weeks	100.0 (83.3, 100.0) (n = 21)	91.7 (50.0, 100.0) (n = 20)	0.23
Change in domain 3 score from baseline to week 24	0.0 (0.0, 33.3) (n = 21)	4.2 (0.0, 37.5) (n = 20)	0.85
Domain 4 score at baseline	50.0 (45.8, 58.3) (n = 21)	54.2 (50.0, 66.7) (n = 20)	0.24
Domain 4 score at 24 weeks	62.5 (54.2, 79.2) (n = 21)	62.5 (50.0, 68.8) (n = 20)	0.56
Change in domain 4 score from baseline to week 24	16.7 (8.3, 25.0)[a] (n = 21)	6.3 (− 4.2, 16.7) (n = 18)	0.15
Each item at 24 weeks (change from baseline)			
Question 1	0.0 (0.0, 2.0) (n = 21)	0.5 (0.0, 2.0) (n = 20)	0.75
Question 2	0.0 (0.0, 1.0) (n = 21)	1.5 (0.0, 3.5) (n = 20)	0.39
Question 3	1.0 (0.0, 3.0) (n = 21)	0.0 (− 1.0, 2.0) (n = 20)	0.43
Question 4	0.0 (0.0, 1.0) (n = 21)	0.0 (0.0, 1.0) (n = 20)	0.88
Question 5	0.0 (0.0, 2.0) (n = 21)	0.0 (0.0, 1.0) (n = 20)	0.29
Question 6	0.0 (0.0, 3.0) (n = 21)	0.0 (0.0, 1.0) (n = 20)	0.27
Question 7	0.0 (0.0, 2.0) (n = 21)	0.5 (− 1.0, 3.0) (n = 20)	0.99
Question 8	0.0 (0.0, 2.0) (n = 21)	0.5 (− 0.5, 3.0) (n = 20)	0.61
Question 9	0.0 (− 1.0, 1.0) (n = 21)	0.0 (− 1.0, 2.0) (n = 20)	0.72
Question 10	1.0 (0.0., 3.0) (n = 21)	0.0 (− 0.5, 1.5) (n = 20)	0.15
Question 11	1.0 (0.0, 2.0) (n = 21)	1.0 (− 0.5, 2.0) (n = 20)	0.33

Table 4 continued

Parameters	Linagliptin group	Metformin group	*P* value (between groups)
Question 12	0.0 (0.0, 3.0) (n = 21)	0.0 (0.0, 1.0) (n = 20)	0.17
Question 13	0.0 (0.0, 3.0) (n = 21)	0.0 (− 1.0, 2.0) (n = 20)	0.21
Question 14	1.0 (0.0, 2.0) (n = 21)	0.0 (0.0, 2.5) (n = 20)	0.27
Question 15	0.0 (− 1.0, 3.0) (n = 21)	0.5 (0.0, 2.0) (n = 20)	0.67
Question 16	0.0 (0.0, 1.0) (n = 21)	0.0 (− 0.5, 2.5) (n = 20)	0.80
Question 17	0.0 (0.0, 3.0) (n = 21)	0.0 (0.0, 2.5) (n = 20)	0.73
Question 18	0.0 (0.0, 3.0) (n = 21)	0.0 (− 0.5, 2.5) (n = 20)	0.62
Question 19	0.0 (0.0, 2.0) (n = 21)	0.0 (0.0, 1.0) (n = 20)	0.52
Question 20	1.0 (0.0, 2.0) (n = 21)	0.5 (− 0.5, 3.0) (n = 20)	0.73
Question 21	2.0 (0.0, 2.0) (n = 21)	0.0 (− 1.0, 2.0) (n = 20)	0.40
Question 22	1.0 (0.0, 3.0) (n = 21)	0.0 (− 2.0, 1.0) (n = 20)	0.03
Question 23	1.0 (0.0, 2.0) (n = 21)	1.0 (− 1.5, 2.0) (n = 20)	0.29
Question 24	0.0 (0.0, 2.0) (n = 21)	0.0 (− 0.5, 1.0) (n = 20)	0.51
Question 25	1.0 (0.0, 2.0) (n = 21)	0.0 (0.0, 1.0) (n = 20)	0.17
Question 26	2.0 (0.0, 3.0) (n = 21)	1.0 (0.0, 2.0) (n = 19)	0.26
Question 27	1.0 (0.0, 2.0) (n = 21)	0.0 (− 1.0, 1.0) (n = 19)	0.21
Question 28	0.0 (0.0, 1.0) (n = 21)	0.0 (− 1.0, 1.0) (n = 18)	0.86
Question 29	2.0 (0.0, 3.0) (n = 21)	1.0 (0.0, 2.0) (n = 18)	0.42

Data are presented as the median with the IQR in parenthesis

Differences between groups at baseline and at 24 weeks were analyzed using the Wilcoxon rank-sum test. Intragroup differences in the change from baseline to 24 weeks were analyzed using the Wilcoxon signed-rank test. Intergroup differences in the change from baseline to 24 weeks were analyzed using the Wilcoxon rank-sum test

[a] $P < 0.01$

associated with OHA-Q score (Pearson's correlation coefficient 0.40; $P = 0.022$) and the subscale 1 score (Pearson's correlation coefficient 0.52;$P = 0.002$).

DISCUSSION

Linagliptin and metformin provide clinically meaningful improvement in glycemic control with an acceptable side effect profile and a low risk of hypoglycemia. The results of this study demonstrated that the linagliptin and metformin groups had similar overall OHA-Q scores, although the linagliptin group had a significantly higher subscale 1 (treatment convenience) score than the metformin group. While overall DTR-QOL scores were comparable between the groups, scores for approximately half of the DTR-QOL items significantly improved after 24 weeks of linagliptin treatment. However, this study did not show that linagliptin was superior to metformin in terms of treatment-related QOL. Nonetheless, linagliptin did not have a negative impact on any aspects of treatment-related QOL compared

with metformin, but rather had a positive impact on several aspects of treatment-related QOL.

Previous studies have reported that the initiation of diabetes treatment is associated with improvements in QOL as assessed by various types of patient-reported outcome evaluations [28, 29, 30]. Consistent with these findings, we found that the overall DTR-QOL questionnaire score was significantly higher after 24 weeks of linagliptin treatment. DPP-4 inhibitors are generally safe and well tolerated. They do not increase body weight and have a low risk for hypoglycemia and unacceptable side effects [14]. These characteristics of linagliptin probably contributed the higher QOL reported in the present study, as previous reports have demonstrated that weight gain, hypoglycemic episodes, and other side effects during diabetes treatment negatively affect QOL [30–32]. In addition, linagliptin is a medicine taken once daily. In this regard, recent clinical studies have demonstrated that once-daily dosing is associated with a higher rate of adherence than more frequent dosing [33–36]. Thus, it is not difficult to imagine that the once-daily dosing regimen for linagliptin might place a lower burden on patients' social and daily activities. Accordingly, the DTR-QOL questionnaire scores related to burden on social activities and daily activities, anxiety, and dissatisfaction with treatment, hypoglycemia, and satisfaction with treatment significantly improved after the initiation of linagliptin treatment. Although such improvements were not found in the metformin group, the DTR-QOL questionnaire score did increase from 64.4 at baseline to 70.2 at the end of study in the metformin group. Metformin is also generally safe, well tolerated, and inexpensive [8]; in fact, the score for question 29 ("With regards to diabetes treatment, I am satisfied with current treatment methods") improved significantly at 24 weeks. Taken together, both linagliptin and metformin are reasonable OHAs from the QOL perspective.

Even though both linagliptin and metformin have the potential to improve treatment-related QOL, patients in the linagliptin group were more likely to be satisfied with their treatment than those in the metformin group. However, the reduction in HbA1c level in the linagliptin group was similar to that in the metformin group. In particular, the linagliptin group had a significantly higher subscale 1 (treatment convenience) score than the metformin group. Similarly, Ishii et al. demonstrated that DPP-4 inhibitors are the most favorable option among the four classes of OHAs (DPP-4 inhibitors, metformin, α-glucosidase inhibitors, and sulfonylureas) as first-line therapy, in terms of improving treatment satisfaction [37]. In contrast, they found that a significantly higher overall OHA-Q score in the DPP-4 inhibitor group than in the metformin group over a 4-week treatment period. The differences in results may be due to differences in study design and the length of the observation period. In the present study, we directly compared the influence of a specific DPP-4 inhibitor, linagliptin, with that of metformin on treatment-related QOL for a longer duration.

Significant differences were observed between the two treatment groups in terms of subscale 1 scores for items such as missed dose, difficulty swallowing, interval between taking the agent and a meal, compliance with treatment schedule, number of doses, and taking the agent while not at home. In this study, the majority of patients were taking metformin twice daily according to the study protocol. Increased dosing frequency might result in treatment inconvenience. In addition, the metformin tablet is larger, so patients might experience difficulty in swallowing the metformin tablet. These factors may be associated with increased patient burden and reduced motivation to comply with treatment, leading to worsening of glycemic control in the long term. In fact, subscale 1 (treatment convenience) and overall OHA-Q scores are positively associated with the rate of adherence to medication. These points are very important when choosing OHAs; the American Diabetes Association emphasized the importance of considering patient preferences in addition to efficacy, hypoglycemic risk, impact on weight, potential side effects, and cost [38].

Despite differences in treatment convenience between the linagliptin and metformin groups, there was no significant difference in

the rate of medication adherence. This unexpected finding might be related to the small sample size, short study duration, and failure to increase the dose of metformin. In particular, the dose of metformin was not increased to $\geq$ 750 mg/day in approximately 80% of patients based on study protocol recommendations. This may be related to investigators' concern about gastrointestinal side effects as the metformin dose increases, although a recent study conducted in Japan showed that increased metformin dosing is not associated with more gastrointestinal side effects [39]. Thus, difficulties in increasing the dose of metformin are also a major barrier to using metformin as first-line therapy in clinical practice in Japan.

There are several limitations to the present study. First, the study was an exploratory study with a relatively small sample size. Second, as this study was limited to subjects not previously taking OHAs, it is not possible to conclude that the effects of linagliptin and metformin on treatment-related QOL can be generalized to patients already on other OHAs. In addition, only one patient with cardiovascular disease were registered in this study. Thus, we could not evaluate the effect of linagliptin versus metformin on treatment-related QOL in patients with cardiovascular disease. Third, we did not assess the long-term effects of these agents on QOL. Finally, we did not consider the influence of the frequency, number, and types of drugs other than OHAs on adherence to study drugs.

In conclusion, we did not find a significant improvement in treatment-related QOL with linagliptin among Japanese patients with T2DM. However, linagliptin did not have a negative impact on any aspects of treatment-related QOL compared with metformin, but rather had a positive impact on several aspects of treatment-related QOL.

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Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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