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ORIGINAL RESEARCH

Therapy-Related Satisfaction and Quality of Life for Japanese People with Diabetes Using Rapid-Acting Insulin Analogs: A Web-Based Survey

Hitoshi Ishii · Yasutaka Maeda · Manaka Sato · Zhihong Cai · Makoto Imori

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ABSTRACT

Introduction: People with diabetes require insulin to regulate blood glucose (BG); rapid-acting insulin analogs (RAIA) represent one approach for BG management. New fast-acting RAIA administered at the start of a meal suppress postprandial BG better than conventional RAIA. New RAIA are expected to confer higher treatment satisfaction and improved quality of life (QOL) than conventional RAIA.

Methods: This cross-sectional, web-based survey in Japan (November 2022) included people with diabetes (type 1/2), aged ≥ 18 years, registered in the Rakuten Insight Diabetes Panel, using new and/or conventional RAIA. RAIA-specific satisfaction was evaluated by questions on RAIA use (scores: 1 [not at all satisfied]; 7 [very satisfied]) and QOL by the Diabetes Therapy-Related (DTR)-QOL questionnaire (scores: 0–100, 100 = best) for the whole population (primary endpoint) and for new versus conventional RAIA users (secondary endpoint). Multiple regression models were used to compare new versus conventional RAIA users.

Results: The analysis population comprised 217 people with diabetes (new RAIA, $n = 109$; conventional RAIA, $n = 108$). Mean (standard deviation) RAIA-specific satisfaction scores ranged from 5.1 (1.2) to 5.4 (1.2); DTR-QOL total score was 51.6 (20.4). RAIA satisfaction scores were numerically higher for new versus conventional RAIA users; no difference in DTR-QOL total score was observed. DTR-QOL satisfaction with treatment domain score was significantly higher in new versus conventional RAIA users (least squares mean difference [standard error]: 7.3 [3.1]; 95% confidence interval: 1.2, 13.4; $P = 0.0197$). RAIA-specific satisfaction was higher among patients who discussed BG sufficiently with their doctor versus those who did not.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-024-01584-9.

H. Ishii
Department of Doctor-Patient Relationships, Nara Medical University, Nara, Japan
e-mail: hit3910@gmail.com

Y. Maeda
Patient Author; Clinic Masae Minami, Fukuoka, Japan
e-mail: myas555@gmail.com

M. Sato (✉) · Z. Cai · M. Imori
Japan Drug Development & Medical Affairs, Eli Lilly Japan K.K., Lilly Plaza One Bldg., 5-1-28, Isogamidori, Chuo-ku, Kobe 651-0086, Japan
e-mail: sato_manaka@lilly.com

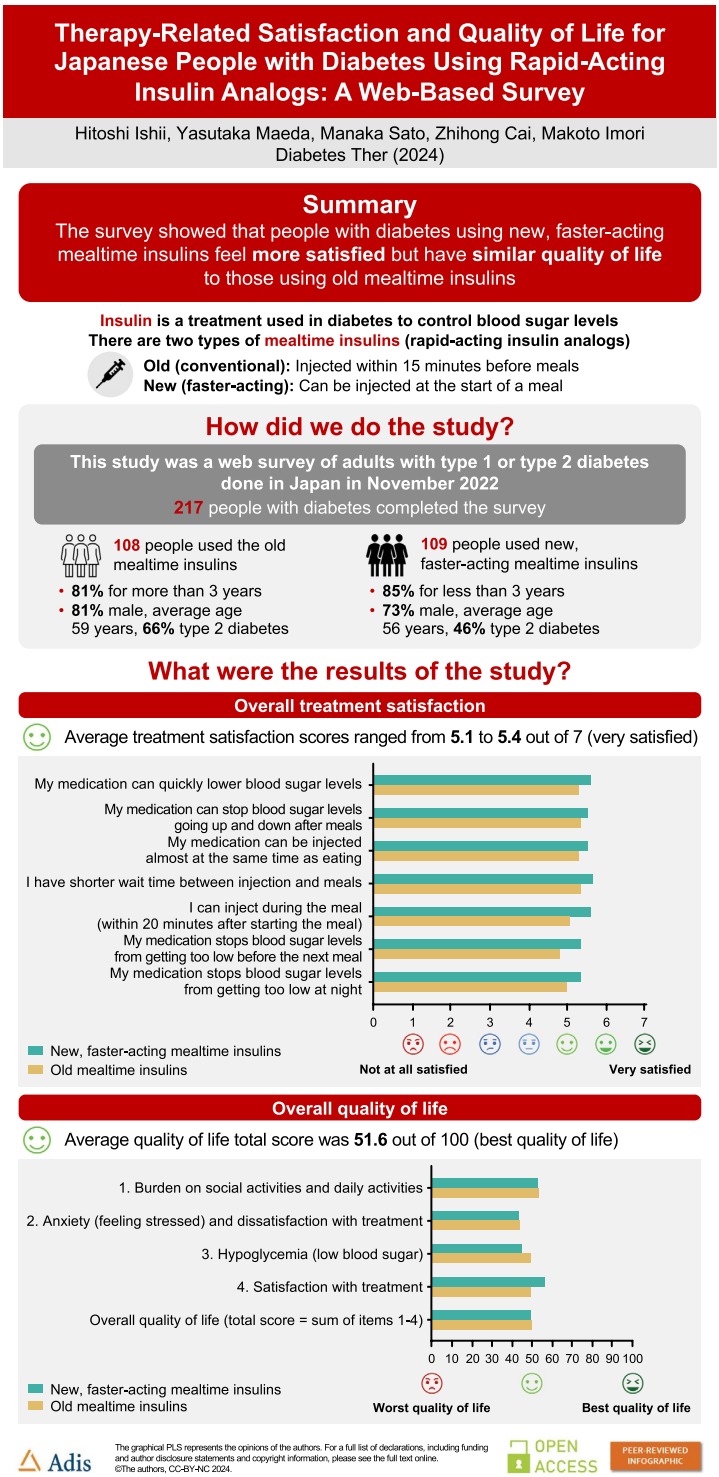
Z. Cai
e-mail: cai_zhihong@lilly.com

M. Imori
e-mail: imori_makoto@lilly.com

Conclusions: New RAIA users have greater treatment satisfaction than conventional RAIA users. QOL was similar among new and conventional RAIA users, except for satisfaction with treatment, which was significantly higher among new RAIA users. Detailed explanations from the doctor to the person with diabetes about the relationship between new RAIA and BG status are essential.

A graphical plain language summary is available with this article.

Graphical Plain Language Summary:



Keywords: Diabetes mellitus; Diabetes Therapy-Related Quality of Life questionnaire; Insulin aspart; Insulin glulisine; Insulin lispro; Japan; Quality of life; Rapid-acting insulin analog; Treatment satisfaction

Key Summary Points
Why carry out this study?
Treatment with rapid-acting insulin analogs (RAIA) is one approach for managing blood glucose in people with diabetes.
New RAIA are faster-acting and suppress postprandial blood glucose better than conventional RAIA when administered at the start of a meal.
Therefore, new RAIA are expected to confer higher treatment satisfaction and improved quality of life (QOL) in people with diabetes than conventional RAIA.
What was learned from the study?
People with diabetes using new RAIA treatments have greater treatment satisfaction than people using conventional RAIA treatments; QOL was similar among new RAIA users and conventional RAIA users, except for satisfaction with treatment, which was significantly higher among new RAIA users.
For better treatment satisfaction, detailed explanations from the doctor to the person with diabetes about the relationship between new RAIA and blood glucose status are essential.

DIGITAL FEATURES

This article is published with digital features, including a graphical plain language summary, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.25407607.

INTRODUCTION

Diabetes is a chronic condition that occurs when either the body cannot effectively use insulin or when the pancreas does not produce enough insulin; insulin is required for regulating blood glucose (BG) levels [1]. In 2021, 537 million adults worldwide were living with diabetes, equating to approximately one in ten adults, with this number predicted to rise to 643 million by 2030 [2]; the age-adjusted comparative prevalence was 9.8% [2]. In Japan, 11 million people were living with diabetes and the age-adjusted comparative prevalence was 6.6% [2].

The current standard of care in diabetes indicates that insulin therapy, such as insulin analogs, is one approach for the management of BG [3–5]. Conventional rapid-acting insulin analogs (RAIA), including insulin lispro, insulin aspart, and insulin glulisine, are administered within 15 min before starting a meal [6–11], with one study indicating that administration 15 min before a meal is best for suppression of postprandial BG [12]. In recent years, new RAIA, such as ultra-rapid lispro (URLi) and fast-acting insulin aspart, have become available and have been shown to be noninferior to conventional RAIA in terms of glycemic control, and superior in terms of postprandial glucose excursions [13, 14], more closely matching the glucose control observed in people without diabetes [15]. As new RAIA suppress postprandial BG better than conventional RAIA [13, 14], new RAIA have the advantage of administration at the start of a meal or within 20 min of starting a meal [16–19]. Quality of life (QOL) in users of conventional RAIA has been assessed [20–29]; however, these studies are now more than 10 years old, and new RAIA are expected to confer higher treatment satisfaction and improved QOL compared with conventional RAIA.

This cross-sectional, web-based survey investigated RAIA-specific satisfaction and QOL in people with diabetes who are using new RAIA and/or conventional RAIA. Furthermore, RAIA-specific satisfaction and QOL by timing of BG level checks was assessed.

METHODS

Study Design

This study was a cross-sectional, web-based survey conducted in Japan in November 2022. A study invitation e-mail was sent from the survey operator (Rakuten Insight Inc., Tokyo, Japan) to people who had registered their disease as diabetes in the Rakuten Insight Diabetes Panel. To register as a 'potential participant' of the survey, participants were required to access and read the electronic Informed Consent Form (eICF), agree to join the study after reading the eICF, consent to publication of the study results, and give their voluntary web-based agreement; a compensation fee (shopping points) for cooperating in the study was supplied to participants. In the first section of the study questionnaire, questions confirming if the potential participant met all the eligibility criteria were asked; those who met eligibility criteria were defined as 'study participants' and those who did not meet the criteria were excluded. Participants could be withdrawn from the study if it was obvious that a participant had not answered questions honestly (for example, those who answered all the questions with number 1, or who finished all the questions in a very short time), when a participant requested withdrawal from the study, or when a participant violated the selection criteria. All personally identifiable information was masked by the survey operator. The study was approved by the Takahashi Clinic Ethics Committee (approval number: LNW00171) and was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki of 1964 and its later amendments, and that are consistent with Ethical Guidelines for Medical and Biological Research Involving Human Subjects, and Japanese laws and regulations.

Study Population

Individuals were included in the study if they were aged ≥ 18 years, had been diagnosed with type 1 or type 2 diabetes, were using new RAIA (URLi [Eli Lilly and Company] and fast-acting insulin aspart [Novo Nordisk]), and/or conventional RAIA (insulin lispro [Eli Lilly and Company], insulin aspart [Novo Nordisk], insulin glulisine [Sanofi], and biosimilar products), and were able to participate in a web-based survey. Individuals were excluded from the study if they had been diagnosed with gestational diabetes.

Survey Items

Demographic and participant background information was collected, including age, sex, body mass index (BMI), type(s) of diabetes, diabetes duration, hemoglobin A1c (HbA1c), diabetes complications (retinopathy, nephropathy, neuropathy, cerebral infarction, angina pectoris/myocardial infarction, peripheral arterial disease, or others), type of RAIA (new RAIA or conventional RAIA, and their biosimilar products), and family members living with the participant.

To evaluate treatment satisfaction, custom RAIA-specific satisfaction questions related to RAIA use were asked (see Supplementary Material). Each question was rated on a seven-point Likert scale, with 1 indicating the highest satisfaction and 7 indicating the lowest satisfaction. When conducting the analysis, the score for each question was reversed so that 7 represents the highest satisfaction: 1. Not at all satisfied; 2. Not satisfied; 3. Not satisfied very much; 4. Neither satisfied nor not satisfied; 5. Satisfied a little; 6. Satisfied; 7. Very satisfied. Other custom questions to assess QOL and satisfaction with treatment by timing of when BG levels were checked and by patient–doctor communication regarding glycemic status in new RAIA users and conventional RAIA users were included (see Supplementary Material).

To assess the influence of diabetes treatment on participant's QOL, regardless of treatment method, the disease-specific, self-administered, Diabetes Therapy-Related (DTR)-QOL questionnaire was used [30]. The DTR-QOL consists of four domains: 1. Burden on social activities and daily activities (13 items); 2. Anxiety and dissatisfaction with treatment (eight items); 3. Hypoglycemia (four items); and 4. Satisfaction with treatment (four items). Questions are rated on a

seven-point Likert scale (1: strongly agree to 7: strongly disagree), with higher scores indicating higher QOL (scores for the four items in the 'satisfaction with treatment' domain are reversed; 1: strongly disagree to 7: strongly agree) [30]. Calculations for DTR-QOL were conducted as described previously [30]; in summary, after simple addition of the item scores, the total score was converted to 0–100 with 100 representing the best score. The domain score was calculated as the mean score of the attribute items within the domain, and the scoring range was converted to 0–100.

Statistical Analysis

The planned sample size was 200 people with diabetes, including 100 new RAIA users and 100 conventional RAIA users. The sample size for new RAIA users was set as a 'potentially achievable size', based on data obtained in a feasibility check, whereas the size for conventional RAIA users was determined based on discussion with the Panel Survey Operator and Questionnaire Designer. The survey was stopped when each group reached 100 individuals with diabetes to ensure equal proportions of new and conventional RAIA users were included in the analysis population.

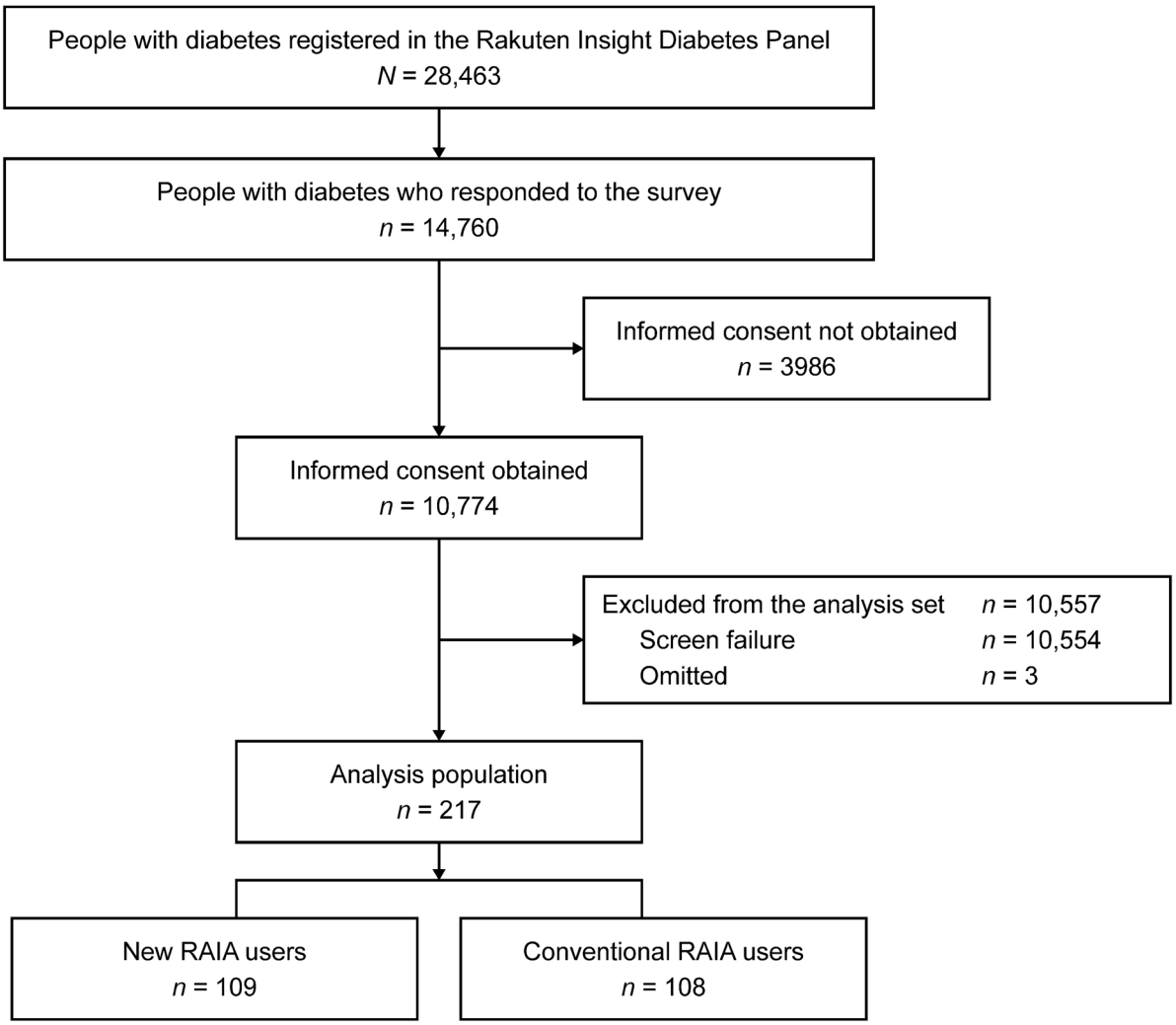


Fig. 1 Participant flow. *RAIA* rapid-acting insulin analog

Table 1 Demographic and clinical characteristics of participants

Characteristic	All ($N = 217$)	New RAIA users[a] ($N = 109$)	Conventional RAIA users[b] ($N = 108$)	*P* value
Age (years)				
Mean (SD)	57.3 (11.8)	55.9 (12.9)	58.8 (10.4)	0.0700[c]
Sex				
Male	168 (77.4)	80 (73.4)	88 (81.5)	0.1940[d]
Female	49 (22.6)	29 (26.6)	20 (18.5)	
BMI (kg/m^2)				
Mean (SD)	24.7 (5.3)	24.1 (4.8)	25.25 (5.8)	0.1206[c]
Family members living together				
Yes	158 (72.8)	89 (81.7)	69 (63.9)	0.0038[d]
No	59 (27.2)	20 (18.3)	39 (36.1)	
Diabetes duration (years)				
n	188	93	95	
Mean (SD)	16.3 (11.6)	14.9 (11.4)	17.7 (11.7)	0.0902[c]
Types of diabetes				
Type 1	88 (40.6)	54 (49.5)	34 (31.5)	0.0130[d]
Type 2	121 (55.8)	50 (45.9)	71 (65.7)	
Other diabetes (except gestational diabetes)	8 (3.7)	5 (4.6)	3 (2.8)	
HbA1c (%)				
n	199	99	100	
Mean (SD)	7.4 (1.0)	7.4 (1.1)	7.3 (1.0)	0.5582[c]
Diabetes complications				
Retinopathy	39 (18.0)	19 (17.4)	20 (18.5)	0.8613[d]
Nephropathy	24 (11.1)	11 (10.1)	13 (12.0)	0.6715[d]
Neuropathy	20 (9.2)	10 (9.2)	10 (9.3)	1.0000[d]
Cerebral infarction	7 (3.2)	5 (4.6)	2 (1.9)	0.4455[d]
Angina pectoris/myocardial infarction	13 (6.0)	4 (3.7)	9 (8.3)	0.1653[d]
Peripheral arterial disease	2 (0.9)	1 (0.9)	1 (0.9)	1.0000[d]
Duration of RAIA use				
< 1 year	–	48 (44.0)	6 (5.6)	–
1 to < 2 years	–	33 (30.3)	7 (6.5)	–
2 to < 3 years	–	12 (11.0)	7 (6.5)	–

Table 1 continued

Characteristic	All ($N = 217$)	New RAIA users[a] ($N = 109$)	Conventional RAIA users[b] ($N = 108$)	*P* value
3 to < 5 years	–	–	15 (13.9)	–
5 to < 10 years	–	–	29 (26.9)	–
10 or more years	–	–	44 (40.7)	–
Missing	–	16 (14.7)	0	–

Data are *n* (%) unless otherwise indicated

BMI body mass index, *HbA1c* hemoglobin A1c, *RAIA* rapid-acting insulin analog, *SD* standard deviation

[a]Ultra-rapid lispro and fast-acting insulin aspart

[b]Insulin lispro, insulin aspart, insulin glulisine, and their biosimilar products

[c]*t* test

[d]Fisher's exact test

Continuous variables were presented as number of participants, mean, standard deviation (SD), minimum, 25th percentile, median, 75th percentile, and maximum; categorical variables were presented as number and percentage. For the primary analysis, descriptive statistics for each question on RAIA-specific satisfaction, and for DTR-QOL total score and for each domain, are presented for the whole population (new and conventional RAIA users combined). For secondary analyses, descriptive statistics for each question about RAIA-specific satisfaction are summarized for new RAIA users and for conventional RAIA users, and the Wilcoxon rank-sum test was used to assess if there was any difference between the two groups. Descriptive statistics for each domain and total score for DTR-QOL are presented for new RAIA users and for conventional RAIA users, and *t* tests were performed to assess if there were any differences between the two groups. Multiple regression models were used to compare RAIA users (new vs. conventional) for each RAIA-specific satisfaction question, and each domain and total score in DTR-QOL scores. Differences of least squares (LS) means (new RAIA – conventional RAIA) and standard error (SE) of the LS means with 95% confidence intervals (CI) and associated *P* values were calculated. To investigate RAIA-specific satisfaction and DTR-QOL scores by whether participants did or did not check BG levels after meals, participants were divided into four subgroups: new RAIA users who checked their BG level after any meal (breakfast, lunch, or dinner); new RAIA users who did not check their BG level after any meal; conventional RAIA users who checked their BG level after any meal; and conventional RAIA users who did not check their BG level after any meal. Multiple regression models were used to compare the timing of BG level checks (after any of the three meals [breakfast, lunch, or dinner] vs. none) for each RAIA-specific satisfaction question, and for each domain and total score of the DTR-QOL, by new RAIA users and conventional RAIA users separately.

For the exploratory analysis to investigate RAIA-specific satisfaction and DTR-QOL scores by communication with doctors, participants were asked "Do you sufficiently discuss your blood sugar test results with your doctor during your consultation?" Response categories were "we discuss sufficiently", "we sometimes discuss", "I am not sure", "we do not discuss very much", and "we do not discuss at all". Mean (SD) scores were summarized and tested by Kruskal–Wallis test and one-way analysis of variance, respectively, for each response category.

For all multiple regression analyses, adjustment factors for bias and confounding were age (continuous variable), sex (male/female), type of diabetes (type 1/type 2, excluding other), and types of BG monitoring systems (self-monitoring blood glucose only, flash glucose monitoring,

Table 2 RAIA satisfaction score and DTR-QOL score in people with diabetes who are using RAIA ($N = 217$)

Items, mean (SD)	All ($N = 217$)	New RAIA users[a] ($N = 109$)	Conventional RAIA users[b] ($N = 108$)	*P* value
RAIA-specific satisfaction score[c]				
1. The rapid-acting insulin analog that you currently use can quickly lower the BG level after administering it	5.4 (1.2)	5.5 (1.2)	5.2 (1.3)	0.0395[d]
2. The rapid-acting insulin analog that you currently use can control postprandial BG spikes	5.4 (1.2)	5.5 (1.2)	5.3 (1.2)	0.1795[d]
3. The rapid-acting insulin analog that you currently use allows you to administer it almost at the same time as you start eating	5.4 (1.2)	5.5 (1.3)	5.2 (1.2)	0.0593[d]
4. The rapid-acting insulin analog that you currently use allows for a shorter wait time between injections and meals, which avoids wasting time	5.4 (1.2)	5.6 (1.2)	5.3 (1.2)	0.0290[d]
5. The rapid-acting insulin analog that you currently use allows you to administer it during the meal (within 20 min after starting the meal)	5.2 (1.3)	5.5 (1.2)	4.9 (1.3)	0.0005[d]
6. The rapid-acting insulin analog that you currently use can control excessive decreases in the BG level before the next meal	5.1 (1.3)	5.2 (1.2)	4.9 (1.4)	0.0550[d]
7. The rapid-acting insulin analog that you currently use can control excessive decreases in the BG level at night time	5.1 (1.2)	5.2 (1.1)	5.0 (1.2)	0.1060[d]
DTR-QOL[c]				
Domain 1: Burden on social activities and daily activities	53.8 (24.9)	52.8 (25.8)	54.9 (24.0)	0.5376[f]
Domain 2: Anxiety and dissatisfaction with treatment	46.8 (23.6)	44.9 (24.0)	48.7 (23.1)	0.2367[f]
Domain 3: Hypoglycemia	50.3 (29.1)	45.9 (28.8)	54.8 (28.9)	0.0238[f]
Domain 4: Satisfaction with treatment	55.2 (21.2)	58.0 (20.2)	52.5 (21.9)	0.0570[f]
Total score	51.6 (20.4)	50.4 (21.3)	52.8 (19.4)	0.3758[f]

BG blood glucose, *DTR-QOL* Diabetes Therapy-Related Quality of Life, *RAIA* rapid-acting insulin analogs, *SD* standard deviation

[a]Ultra-rapid lispro and fast-acting insulin aspart

[b]Insulin lispro, insulin aspart, insulin glulisine, and their biosimilar products

[c]RAIA-specific satisfaction score range: 1. "Not at all satisfied" to 7. "Very satisfied"

[d]Wilcoxon rank-sum test (new RAIA vs. conventional RAIA)

[e]Total score and each domain score = (observed score − minimum possible value) / (maximum possible value − minimum possible value) × 100, with 100 representing the best score

[f]*t* test (new RAIA vs. conventional RAIA)

real-time continuous glucose monitoring [CGM] or professional CGM, excluding participants who were not using a monitoring system). The significance level was two-sided 5%; statistical comparisons of new RAIA users versus conventional RAIA users for participant demographic and clinical characteristics were performed as a post hoc analysis. Missing data were not imputed and no multiplicity adjustment was performed. Analyses were conducted using SAS software, version 9.4 for Windows (SAS Institute, Cary, NC, USA).

RESULTS

Demographic and Clinical Characteristics of Participants

The analysis population consisted of 217 people with diabetes, including 109 new RAIA users and 108 conventional RAIA users (Fig. 1). Most participants who provided informed consent were excluded because of screen failure; three participants who completed the survey were excluded because there was doubt about the accuracy of the answers due to the speed with which they answered the questions. For the analysis population, mean age was 57.3 years, 77.4% of participants were male, and the mean BMI was 24.7 kg/m^2 (Table 1). Mean duration of diabetes was 16.3 years, 40.6% of participants had type 1 diabetes and 55.8% had type 2 diabetes, and mean HbA1c was 7.4%. New RAIAs had been used for < 3 years in at least 85% of participants, whereas conventional RAIAs had been used for > 3 years in 81% of participants. Demographic and clinical characteristics were similar between the new RAIA users and conventional RAIA users except for 'family members living together' and 'type of diabetes', which were both significantly different between new RAIA users and conventional RAIA users (Table 1). The proportion of participants with family members living together (81.7 vs. 63.9%) and the proportion of participants with type 1 diabetes (49.5 vs. 31.5%) were significantly higher for new RAIA users versus conventional RAIA users, respectively. New RAIA users tended to be younger (mean 55.9 vs. 58.8 years, respectively), more often female (26.5 vs. 18.5%, respectively), and with a shorter duration of diabetes (mean 14.9 vs. 17.7 years) than conventional RAIA users (Table 1). Among conventional RAIA users, there was a higher proportion of participants with type 2 diabetes versus type 1 diabetes (65.7 vs. 31.5%, respectively), which differs from that among new RAIA users where the proportions were similar (45.9 vs. 49.5%, type 2 diabetes vs. type 1 diabetes, respectively).

Primary Endpoints

Among the total population, the mean (SD) RAIA-specific satisfaction scores ranged from 5.1 (1.2) to 5.4 (1.2), where a score of 7 represents the highest satisfaction, and the mean (SD) DTR-QOL total score was 51.6 (20.4), where a score of 100 represents the highest health-related QOL (Table 2). Satisfaction scores were highest for questions related to the ability of the RAIA to control postprandial BG spikes, to enable administration at almost the same time as starting a meal, and a shorter wait time between injections and meals. The DTR-QOL domain score for satisfaction with treatment was the highest (mean [SD], 55.2 [21.2]) and the domain score for anxiety and dissatisfaction with treatment was the lowest (mean [SD], 46.8 [23.6]).

Secondary Endpoints

New RAIA Users and Conventional RAIA Users

For unadjusted data, the mean (SD) RAIA satisfaction score for each custom question was numerically higher for new RAIA users compared with conventional RAIA users and was statistically significantly higher for custom question 1, "The rapid-acting insulin analog that you currently use can quickly lower the BG level after administering it" (5.5 [1.2] vs. 5.2 [1.3]; $P = 0.0395$), custom question 4, "The rapid-acting insulin analog that you currently use allows for a shorter wait time between injections and meals, which avoids wasting time" (5.6 [1.2] vs.

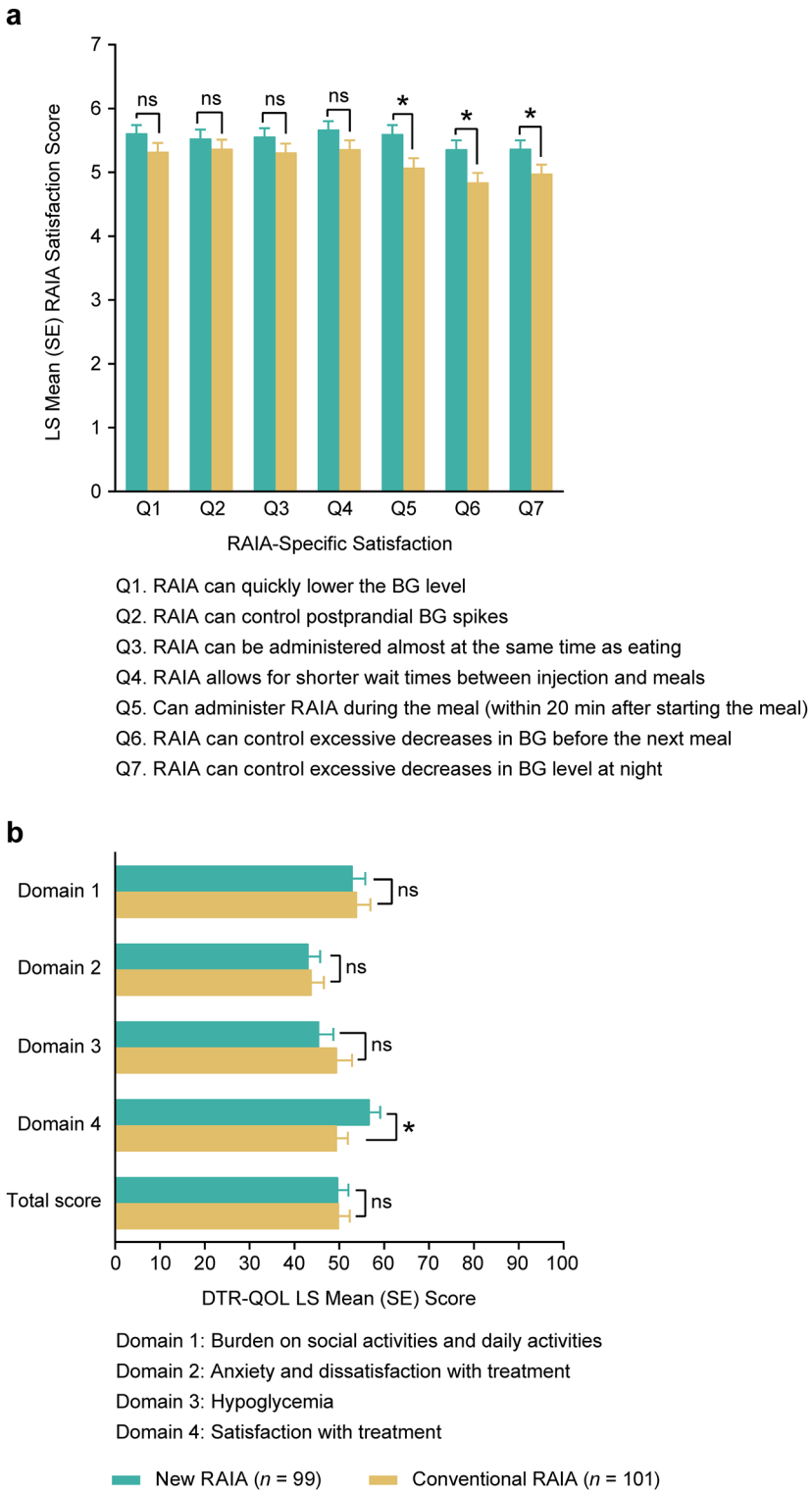
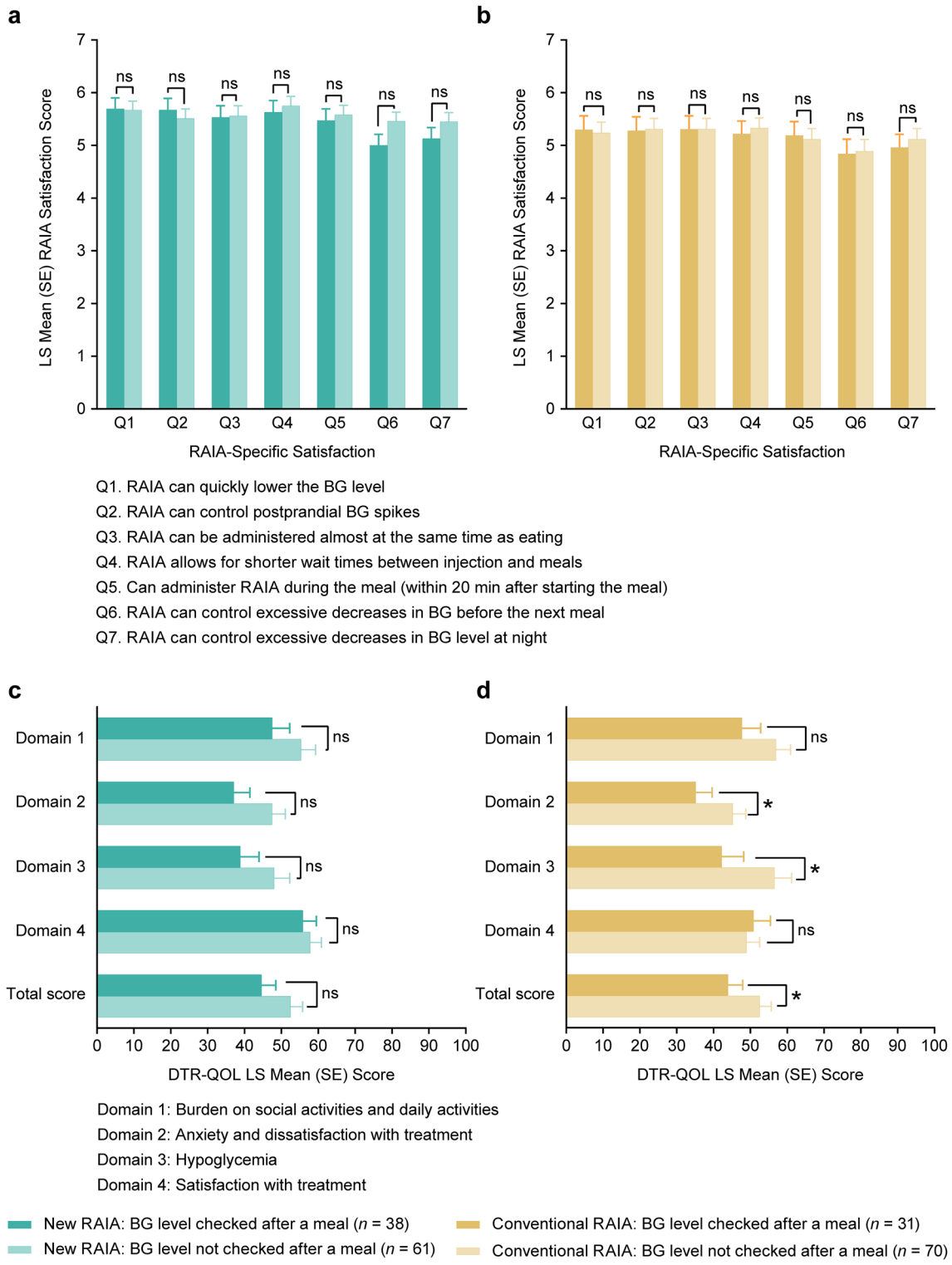


Fig. 2 RAIA satisfaction score (**a**) and DTR-QOL score (**b**) in people with diabetes who are using new RAIA and conventional RAIA (multiple regression model). *$P < 0.05$. *BG* blood glucose, *DTR-QOL* Diabetes Therapy-Related Quality of Life, *LS* least squares, *ns* nonsignificant, *RAIA* rapid-acting insulin analog, *SE* standard error



5.3 [1.2]; $P=0.0290$), and custom question 5, "The rapid-acting insulin analog that you currently use allows you to administer it during the meal (within 20 min after starting the meal)" (5.5 [1.2] vs. 4.9 [1.3]; $P=0.0005$) (Table 2).

◂**Fig. 3** RAIA satisfaction score (**a**, **b**) and DTR-QOL score (**c**, **d**) in people with diabetes who are using new RAIA and conventional RAIA with and without post-meal blood glucose level check at any of the three following times: breakfast, lunch, or dinner (multiple regression model). *$P < 0.05$. *BG* blood glucose, *DTR-QOL* Diabetes Therapy-Related Quality of Life, *LS* least squares, *ns* non-significant, *RAIA* rapid-acting insulin analog, *SE* standard error

After adjustment for confounding factors, RAIA satisfaction score for each custom question was numerically higher for new RAIA users compared with conventional RAIA users (Fig. 2a). Significant differences were observed between the two groups for custom question 5, "The rapid-acting insulin analog that you currently use allows you to administer it during the meal (within 20 min after starting the meal)," (LS mean difference [SE] 0.5 [0.2]; 95% CI 0.2, 0.9; $P=0.0048$), custom question 6, "The rapid-acting insulin analog that you currently use can control excessive decreases in the blood glucose level before the next meal," (LS mean difference [SE] 0.5 [0.2]; 95% CI 0.2, 0.9; $P=0.0066$), and custom question 7, "The rapid-acting insulin analog that you currently use can control excessive decreases in the blood glucose level at night time" (LS mean difference [SE] 0.4 [0.2]; 95% CI 0.1, 0.7; $P=0.0269$).

For unadjusted data, no difference in the DTR-QOL total score was observed between new RAIA users and conventional RAIA users, but there was a significant difference in the DTR-QOL domain score for hypoglycemia (mean [SD]: 45.9 [28.8] vs. 54.8 [28.9], respectively; $P=0.0238$) (Table 2).

After adjustment for confounding factors, no difference in the DTR-QOL total score was observed between new RAIA users and conventional RAIA users, hypoglycemia was no longer significantly different between the two groups, but there was a significant difference in the DTR-QOL domain score for satisfaction with treatment (LS mean difference [SE]: 7.3 [3.1]; 95% CI 1.2, 13.4; $P=0.0197$) (Fig. 2b).

Post-Meal Blood Glucose Level Check

There was no difference in RAIA-specific satisfaction scores with or without checking BG level after a meal for both new RAIA users (Fig. 3a) and conventional RAIA users (Fig. 3b). Among new RAIA users, there was no difference in DTR-QOL total score for those who checked BG level after a meal compared with those who did not (Fig. 3c). However, DTR-QOL total score was statistically significantly lower for conventional RAIA users who checked BG level after a meal compared with those who did not (LS mean difference [SE] −8.6 [4.2]; 95% CI −16.9, −0.4; $P=0.0412$) (Fig. 3d). For conventional RAIA users, DTR-QOL domain scores for anxiety and dissatisfaction with treatment and hypoglycemia were statistically significantly lower for those who did check BG level after a meal compared with those who did not (LS mean difference [SE] −10.1 [4.7]; 95% CI −19.3, −0.8; $P=0.0333$; and LS mean difference [SE] −14.3 [6.2]; 95% CI −26.6, −2.0; $P=0.0235$, respectively).

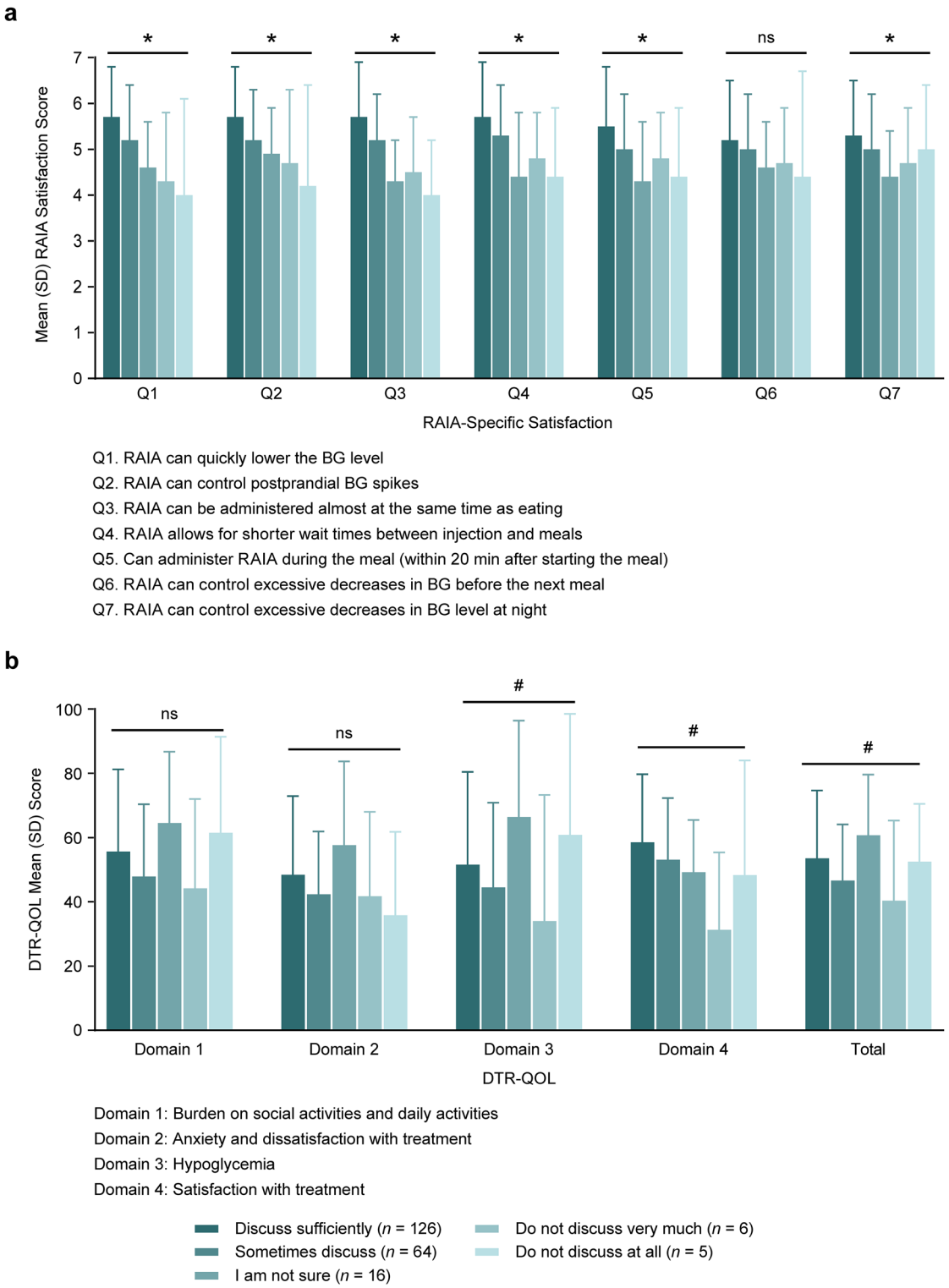
Exploratory Endpoint

Communication with Doctors

There was a statistically significant difference in most satisfaction scores across the levels of reported communication with doctors regarding glycemic status (Fig. 4a). Satisfaction was numerically higher among participants who discussed BG levels sufficiently with their doctor compared with those who did not (Fig. 4a); no significant difference was observed for custom question 6, "The rapid-acting insulin analog that you currently use can control excessive decreases in the blood glucose level before the next meal". The DTR-QOL domain score for satisfaction with treatment was numerically higher among participants who did discuss BG levels sufficiently with the doctor compared with those who did not (Fig. 4b).

DISCUSSION

This cross-sectional, web-based survey is the first study to assess treatment satisfaction and QOL in people with diabetes who are users of new or conventional RAIA in the real-world



setting in Japan. In the whole study population (new and conventional RAIA users combined), RAIA-specific satisfaction scores were high but DTR-QOL scores were not [30, 31]. RAIA-specific

◂**Fig. 4** RAIA satisfaction score (**a**) and DTR-QOL score (**b**) in people with diabetes who are using RAIA by communication with their doctor regarding glycemic status. Domain 1: Burden on social activities and daily activities. Domain 2: Anxiety and dissatisfaction with treatment. Domain 3: Hypoglycemia. Domain 4: Satisfaction with treatment. *$P < 0.05$ Kruskal–Wallis test. #$P < 0.05$ one-way ANOVA. *ANOVA* analysis of variance, *BG* blood glucose, *DTR-QOL* Diabetes Therapy-Related Quality of Life, *LS* least squares, *ns* nonsignificant, *RAIA* rapid-acting insulin analog, *SE* standard error

satisfaction scores were numerically higher for new RAIA users compared with conventional RAIA users and were significantly higher for questions related to administration of the RAIA during a meal, for controlling excessive decreases in BG level before the next meal, and for controlling excessive decreases in BG level at night time. There was no difference in the DTR-QOL total score between new and conventional RAIA users; however, after adjustment for confounding factors, the score for the DTR-QOL domain satisfaction with treatment was significantly higher for users of new RAIA compared with conventional RAIA users. Furthermore, DTR-QOL for the domain satisfaction with treatment was higher for participants who discussed sufficiently their BG levels with their doctor compared with those who did not.

In the current study, self-monitoring of BG levels did not affect RAIA-specific satisfaction. No difference in RAIA-specific satisfaction was observed between participants who do conduct post-meal BG level checks compared with those who do not; results were consistent for new and conventional RAIA users. These results suggest that the participants lacked knowledge and information about BG, which is thought to be affecting their satisfaction with treatment. However, participants were able to realize the benefit of RAIA treatment when they had discussed sufficiently with their doctor about the relationship between their BG status and their RAIA treatment. Therefore, it is considered important for physicians who have the knowledge and information about BG to communicate and discuss this with their patients.

The DTR-QOL domain score for satisfaction with treatment—which includes four questions related to current glycemic control, maintaining good glycemic control with current treatment, hope about the future with current treatment, and satisfaction with current diabetes treatment—was significantly higher for new RAIA users compared with conventional RAIA users; DTR-QOL total scores were similar between new versus conventional RAIA users. For both new and conventional RAIA users, there was a trend for higher DTR-QOL scores among those participants who did not check their post-meal BG level compared with those who did. For conventional RAIA users, DTR-QOL domain scores for anxiety and dissatisfaction with treatment, hypoglycemia, and DTR-QOL total score were significantly lower for participants who did check their post-meal BG compared with those who did not. The lower QOL observed for participants who did check their post-meal BG level may be the result of those individuals feeling anxious, worried, or scared of the varied results of their post-meal BG (i.e., BG levels were not within desired/expected range), it may have been difficult for them to realize postprandial BG decreased with RAIA treatment, or lastly, it may be inconvenient for people with diabetes to measure their post-meal BG leading to the lower DTR-QOL scores.

We evaluated RAIA-specific satisfaction and QOL by the level of communication with the doctor regarding glycemic status. For all custom questions, including those not related to BG, RAIA-specific satisfaction was higher in those participants who discussed glycemic status and injection timing with meals sufficiently with their doctor, including those questions that were not related to BG. Therefore, it is important for doctors to discuss not only BG but also the timing of RAIA injections and their relationship with meals. This will improve the understanding of new RAIA treatments and further improve the QOL of people with diabetes. With regards to QOL, satisfaction with treatment was higher for those who did discuss BG levels sufficiently with the doctor, but QOL related to hypoglycemia tended to be higher for those participants who did not discuss BG levels at all compared with those who did. However, the number of

participants who did not discuss BG levels at all was very small ($n=5$), so it is hard to draw firm conclusions; nevertheless, most participants felt that they did discuss BG levels sufficiently with their doctors. Overall, these results indicate that RAIA-specific satisfaction and QOL scores increase with greater communication with the treating doctor. Within these discussions with the doctor, the person with diabetes should receive an explanation about the effects of new RAIA treatment on BG and the timing of RAIA injections, which may enable the person to recognize the benefits of new versus conventional RAIA treatment.

This study assessed treatment satisfaction using custom questions and QOL using a validated diabetes-specific questionnaire and is strengthened by the large sample size (>200 people with diabetes) consisting of both new RAIA users and conventional RAIA users. This study included people with type 1 diabetes and people with type 2 diabetes; although we did adjust for 'type of diabetes' in the multiple regression analysis, we acknowledge that the pathophysiology, disease history, and experience for people with type 1 diabetes are distinct from those with type 2 diabetes. In this study, multiplicity adjustment was not conducted because these results are exploratory, and nonvalidated custom questions were included in the survey. Furthermore, the study is not representative of all people with diabetes in Japan, because not all people with diabetes in Japan have registered their disease with the survey operator. A response bias because participation was not mandatory and a selection bias as highly motivated people with diabetes were more likely to participate may have occurred. There may have been selection bias for new RAIA and conventional RAIA users that was not completely adjusted for, as well as bias for people who check post-meal BG because pre-meal BG check is considered general practice for people with diabetes. Post hoc analyses of demographic and clinical characteristics indicated a significant difference for the proportion of participants with 'family members living together' between new RAIA users and conventional RAIA users. However, we did not consider 'family members living together' for adjustment, and this may have affected the study results. Moreover, we did not consider and report the number of RAIA injections in a day, and this could have an impact on treatment satisfaction or QOL. Lastly, CGM usage and nutrition (especially the amount of carbohydrate and the carbohydrate-to-fat ratio) have been shown to have a greater effect on postprandial glucose response than insulin in a prediction model of people with type 1 diabetes [32]. Similarly, consumption of carbohydrates in Western countries tends to be lower in comparison with the target carbohydrate rate recommended by the Japan Diabetes Society (approximately 40% vs. recommended 50–60%) [33, 34]. In this study, we adjusted for CGM usage but not for carbohydrate intake because data related to nutrition were not collected.

CONCLUSIONS

The present study suggests that people with diabetes using new RAIA treatments have greater treatment satisfaction than people using conventional RAIA treatments. Furthermore, QOL was similar among new RAIA users and conventional RAIA users, except for QOL related to satisfaction with treatment, which was significantly higher among new RAIA users. Administering new RAIA and measuring post-meal BG in addition to pre-meal BG is not sufficient for people with diabetes to realize the benefit of new RAIA, and detailed explanations from the doctor to the person with diabetes about the relationship between new RAIA and BG status are essential.

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

Declarations

Conflict of Interest. Hitoshi Ishii declares lecture fees from Eli Lilly Japan K.K., Novo Nordisk, MSD K.K., and Sumitomo Pharma Co. Ltd. Manaka Sato, Zhihong Cai, and Makoto Imori are employees of Eli Lilly Japan K.K., and are minor stockholders of Eli Lilly and Company. Yasutaka Maeda has nothing to declare.

Ethical Approval. The study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments, and is consistent with Ethical Guidelines for Medical and Biological Research Involving Human Subjects, and Japanese laws and regulations. The study was approved by the Takahashi Clinic Ethics Committee (approval number: LNW00171). All participants provided electronic informed consent to participate in the study and for the publication of the study results.

REFERENCES

1. World Health Organization: Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes (2023). Accessed 18 July 2023.

2. International Diabetes Federation: IDF Diabetes Atlas, 10th edn. Brussels, Belgium, 2021. https://www.diabetesatlas.org (2022). Accessed 18 July 2023.

3. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753–86. https://doi.org/10.2337/dci22-0034.

4. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Introduction and methodology: standards of care in diabetes—2023. Diabetes Care. 2022;46(Suppl 1):S1–4. https://doi.org/10.2337/dc23-Sint.

5. Holt RIG, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2021;64(12):2609–52. https://doi.org/10.1007/s00125-021-05568-3.

6. Eli Lilly and Company: HUMALOG (insulin lispro injection). Prescribing information. https://uspl.lilly.com/humalog/humalog.html#pi (2023). Accessed 20 July 2023.

7. Novo Nordisk Inc.: NovoRapid® (insulin aspart). Package information. https://media.mycme.com/documents/42/novorapid_pi_august_2012_10451.pdf (2012). Accessed 20 July 2023.

8. Sanofi-Aventis U.S. LLC.: APIDRA® (insulin glulisine injection). https://products.sanofi.us/apidra/apidra.html (2019). Accessed 20 July 2023.

9. Pharmaceuticals and Medical Devices Agency: Apidra® vial S.C. Injection [package insert] [Japanese]. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/780069_2492418A1024_1_10 (2020). Accessed 24 Aug 2023.

10. Pharmaceuticals and Medical Devices Agency: NovoRapid® Injection 100 U/mL [package insert] [Japanese]. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/620023_2492415A3031_1_10 (2020). Accessed 24 Aug 2023.

11. Pharmaceuticals and Medical Devices Agency: Humalog® Injection [package insert] [Japanese]. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/530471_2492414A2030_1_17 (2020). Accessed 24 Aug 2023.

12. Rassam AG, Zeise TM, Burge MR, Schade DS. Optimal administration of lispro insulin in hyperglycemic type 1 diabetes. Diabetes Care. 1999;22(1):133–6. https://doi.org/10.2337/diacare.22.1.133.

13. Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM, PRONTO-T2D Investigators. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. Diabetes Care. 2020;43(12):2991–8. https://doi.org/10.2337/dc19-2550.

14. Klaff L, Cao D, Dellva MA, Tobian J, Miura J, Dahl D, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. Diabetes Obes Metab. 2020;22(10):1799–807. https://doi.org/10.1111/dom.14100.

15. Heise T, Linnebjerg H, Coutant D, LaBell E, Zijlstra E, Kapitza C, et al. Ultra rapid lispro lowers postprandial glucose and more closely matches normal physiological glucose response compared to other rapid insulin analogues: a phase 1 randomized, crossover study. Diabetes Obes Metab. 2020;22(10):1789–98. https://doi.org/10.1111/dom.14094.

16. Eli Lilly and Company: LYUMJEV (insulin lispro-aabc) injection. Prescribing information. https://uspl.lilly.com/lyumjev/lyumjev.html#pi (2022). Accessed 20 July 2023.

17. Novo Nordisk Inc.: FIASP® (insulin aspart) injection. Prescribing information. https://www.novo-pi.com/fiasp.pdf (2023). Accessed 20 July 2023.

18. Pharmaceuticals and Medical Devices Agency: Fiasp® Injection 100 U/mL [package insert] [Japanese]. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/620023_2492415A5026_1_05 (2023). Accessed 24 Aug 2023.

19. Pharmaceuticals and Medical Devices Agency: LYUMJEV® Injection [package insert] [Japanese]. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/530471_2492414A7024_1_05 (2022). Accessed 24 Aug 2023.

20. Masuda H, Sakamoto M, Irie J, Kitaoka A, Shiono K, Inoue G, et al. Comparison of twice-daily injections of biphasic insulin lispro and basal-bolus therapy: glycaemic control and quality-of-life of insulin-naïve type 2 diabetic patients. Diabetes Obes Metab. 2008;10(12):1261–5. https://doi.org/10.1111/j.1463-1326.2008.00897.x.

21. Kawamura T, Urakami T, Sugihara S, Kim HS, Mochizuki M, Amamiya S. Changes in glycemic control and quality of life in pediatric type 1 diabetics with continuous subcutaneous insulin infusion of insulin aspart following multiple daily injection therapy. Clin Pediatr Endocrinol. 2008;17(2):39–47. https://doi.org/10.1297/cpe.17.39.

22. Ishii H, Anderson JH Jr, Yamamura A, Takeuchi M, Ikeda I. Improvement of glycemic control and quality-of-life by insulin lispro therapy: assessing benefits by ITR-QOL questionnaires. Diabetes Res Clin Pract. 2008;81(2):169–78. https://doi.org/10.1016/j.diabres.2008.03.020.

23. Ashwell SG, Bradley C, Stephens JW, Witthaus E, Home PD. Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. Diabetes Care. 2008;31(6):1112–7. https://doi.org/10.2337/dc07-1183.

24. Kamoi K, Miyakoshi M, Maruyama R. A quality-of-life assessment of intensive insulin therapy using insulin lispro switched from short-acting insulin and measured by an ITR-QOL questionnaire: a prospective comparison of multiple daily insulin injections and continuous subcutaneous insulin infusion. Diabetes Res Clin Pract. 2004;64(1):19–25. https://doi.org/10.1016/j.diabres.2003.10.005.

25. Bott U, Ebrahim S, Hirschberger S, Skovlund SE. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. Diabet Med. 2003;20(8):626–34. https://doi.org/10.1046/j.1464-5491.2003.01010.x.

26. Gray M, Boland EA, Tamborlane WV. Use of lispro insulin and quality of life in adolescents on intensive therapy. Diabetes Educ. 1999;25(6):934–41. https://doi.org/10.1177/014572179902500611.

27. Campbell RK, Sclar DA, Robison LM, Stowers JK, Ferguson JC, Trippe BS, et al. Impact on clinical status and quality of life of switching from regular insulin to insulin lispro among patients using insulin pumps. Diabetes Educ. 1998;24(1):95–9. https://doi.org/10.1177/014572179802400113.

28. Tubiana-Rufi N, Munz-Licha G. [Lispro analog and quality of life] [French]. Diabetes Metab. 1997;23(Suppl 3):58–62.

29. Kotsanos JG, Vignati L, Huster W, Andrejasich C, Boggs MB, Jacobson AM, et al. Health-related quality-of-life results from multinational clinical trials of insulin lispro. Assessing benefits of a new diabetes therapy. Diabetes Care. 1997;20(6):948–58. https://doi.org/10.2337/diacare.20.6.948.

30. Ishii H. Development and psychometric validation of the Diabetes Therapy-Related QOL (DTR-QOL) questionnaire. J Med Econ. 2012;15(3):556–63. https://doi.org/10.3111/13696998.2012.665111.

31. Ishii H, Takamura H, Nishioka Y, Langer J, Watanabe M, Kim HR, et al. Quality of life and utility values for cost-effectiveness modeling in Japanese patients with type 2 diabetes. Diabetes Ther. 2020;11(12):2931–43. https://doi.org/10.1007/s13300-020-00938-3.

32. Shilo S, Godneva A, Rachmiel M, Korem T, Kolobkov D, Karady T, et al. Prediction of personal glycemic responses to food for individuals with type 1 diabetes through integration of clinical and microbial data. Diabetes Care. 2022;45(3):502–11. https://doi.org/10.2337/dc21-1048.

33. Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, et al. Japanese clinical practice guideline for diabetes 2019. J Diabetes Investig. 2020;11(4):1020–76. https://doi.org/10.1111/jdi.13306.

34. Diabetes Nutrition Study Group of the Spanish Diabetes Association. Diabetes Nutrition and Complications Trial (DNCT): food intake and targets of diabetes treatment in a sample of Spanish people with diabetes. Diabetes Care. 1997;20(7):1078–80. https://doi.org/10.2337/diacare.20.7.1078.