Journal of Obesity & Metabolic Syndrome 2022;31:254-262
https://doi.org/10.7570/jomes22029

Original Article

jomes
pISSN 2508-6235
eISSN 2508-7576

Adherence to and Dropout from Liraglutide 3.0 mg Obesity Treatment in a Real-World Setting

Hae-Jin Ko[1,2], Jin-Wook Kim[3,4], Soo Lim[5,*]

[1]Department of Family Medicine, School of Medicine, Kyungpook National University, Daegu; [2]Department of Family Medicine, Kyungpook National University Hospital, Daegu; [3]Department of Family Medicine, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu; [4]Department of Family Medicine, Korea University College of Medicine, Seoul; [5]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Background: The factors associated with non-adherence to obesity treatment using liraglutide 3.0 mg in a real-world setting remain elusive.

Methods: We performed a secondary data analysis of 769 participants treated with liraglutide 3.0 mg from December 2017 to June 2020 at nine Korean hospitals. Data were collected 2, 4, and 6 months after treatment initiation. Adherence groups were defined as <2, 2–4, 4–6, and ≥6 months.

Results: Among the 769 patients, 539 (70.1%) were lost to follow-up within 6 months because of unknown reasons (54.2%), adverse events (14.8%), change of treatment (13.7%), or discontinuation due to poor weight loss (9.3%). Dropout at 6 months was significantly associated with the presence of diabetes mellitus in step 1 and the presence of diabetes mellitus with regular exercise in step 2 of the logistic regression analysis using the forward stepwise selection method. After adjusting for covariates, the presence of diabetes mellitus (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.10–0.63; OR, 0.47; 95% CI, 0.31–0.73; and OR, 0.52; 95% CI, 0.34–0.80) and regular exercise (OR, 2.86; 95% CI, 1.31–6.23; OR, 2.09; 95% CI, 1.26–3.48; and OR, 2.99; 95% CI, 1.81–4.92) showed significant associations in the <2, 2–4, and 4–6 groups compared with the highest adherence group (≥6 months).

Conclusion: Non-adherence to obesity treatment with liraglutide is related to regular exercise and absence of diabetes mellitus. Further prospective studies are warranted to increase medication adherence in those groups.

Key words: Diabetes mellitus, Exercise, Lost to follow-up, Liraglutide, Medication adherence

Received April 15, 2022
Reviewed June 7, 2022
Accepted August 17, 2022

*Corresponding author
Soo Lim

https://orcid.org/0000-0002-4137-1671

Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-7035
Fax: +82-31-787-4051
E-mail: limsoo@snu.ac.kr

The first two authors contributed equally to this study.

INTRODUCTION

The prevalence of obesity is rapidly increasing worldwide, and South Korea is no exception. More than 1.9 billion adults are obese, and one-third of the global population is overweight or obese.[1] At a body mass index (BMI) cutoff of ≥25 kg/m^2, which defines obesity in Korean adults, the prevalence of obesity was 38.5% in 2018, and the prevalence of class III obesity tripled from 2009 to 2018.[2]

A preliminary loss of 5%–10% of body weight in 6 months is recommended for obesity treatment. Alongside pharmacotherapy, nutritional therapy, physical activity, and behavioral therapy can facilitate weight loss.[3] Liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that is 97% homologous to human glucagon-like peptide-1, is an approved anti-obesity drug for long-term treatment at a dose of 3.0 mg/day. Its efficacy with or without comorbidities has been established.[4-8] However, factors associated with non-adherence to it are largely unknown; in fact, to the best of our knowledge, they have not yet been studied in Korea at all.

Adherence to medication is defined as the extent to which patients follow their healthcare providers' recommendations,[9] and for

patients with chronic diseases, it is linked to disease control, hospital admission rate, morbidity, and even mortality.[10,11] Similarly, adherence to anti-obesity medication is important for achieving and maintaining weight loss. Studies on adherence to anti-obesity medication remain scarce, and the few that have been conducted indicate that adherence is generally poor and varies significantly among drug types.[12] Therefore, we assessed the rate and causes of non-adherence among people with obesity who were treated with liraglutide 3.0 mg in a real-world setting in Korea.

METHODS

Study design and participants

A secondary analysis of real-world data was performed to assess the adherence to liraglutide 3.0 mg for the treatment of obesity, as described in detail elsewhere.[13] Briefly, patients treated with liraglutide for obesity (BMI ≥ 25 kg/m^2) were recruited from December 2017 to June 2020 from nine hospitals in South Korea, and their treatment with 3.0 mg liraglutide daily was followed up by their physicians from its initiation. The index date was defined as the date of liraglutide treatment initiation, and the starting dose was 0.6 mg/day, which was increased weekly by 0.6 mg until the 3.0 mg/day maintenance dose was reached. Data were collected 2, 4, and 6 months after treatment initiation. In line with liraglutide 3.0 mg treatment, the physicians provided their patients with behavioral treatment, an individualized low-calorie diet, and an exercise plan to achieve sufficient weight loss. Anthropometric measurements, laboratory test results, body composition, and any complaints or adverse events were retrospectively collected from electronic medical records. This study protocol was reviewed and approved by the institutional review board of Seoul National University Bundang Hospital (No. B-2103-670-106). Informed consent was waived because of the retrospective design of the study and the analysis used anonymous clinical data.

The inclusion criteria for this study were as follows: (1) obesity (BMI ≥ 25 kg/m^2), (2) age ≥ 17 years, (3) ≥ 1 prescription for liraglutide 3.0 mg, (4) ≥ 1 baseline body weight measurement within 1 month before the index date, (5) ≥ 1 visit to the clinic in the 6 months following the index date, and (6) ≥ 1 obesity-related comorbidity, such as prediabetes, diabetes mellitus, hypertension, dyslipidemia, or fatty liver disease. The exclusion criteria were as follows: (1) administration of any type of GLP-1 RA before the index date, (2) use of other anti-obesity medications (including lorcaserin, orlistat, phentermine, and phentermine-topiramate extended-release), (3) any malignancy, and (4) a history of bariatric or metabolic surgery. Of the 820 patients, 51 were excluded by those criteria.[13]

Demographic characteristics

The baseline characteristics, demographics, smoking status, exercise status, and medical history, on the index date were collected. The participants were divided into non-smokers, ex-smokers, and current smokers. Regular exercise was defined as ≥ 3 times per week and ≥ 30 min/session of moderate-to-vigorous physical activity such as walking, running, badminton, tennis, cycling, swimming, and climbing.

Anthropometric measurements and laboratory tests

Height, body weight, and waist circumference were measured by a regular nurse or physician assistant at every visit, and the BMI was calculated as weight (kg) divided by height squared (m^2). The mean systolic and diastolic blood pressure was derived from two measurements taken in the seated position with a 5-minute interval between them using validated electronic (oscillometric) devices.

The following biochemical parameters were measured from fasting blood samples: glycated hemoglobin (HbA1c), plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine. The estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation.[14]

Adherence and dropout

Data were collected 2, 4, and 6 months after the initiation of liraglutide treatment, and the participants were assigned to different adherence groups according to their treatment and follow-up records: (1) ≤ 2 months (≤ 8 weeks), lost to follow-up within 2 months of the index date; (2) 2–4 months (8–16 weeks), adherent to liraglutide for > 2 months and < 4 months; (3) 4–6 months (16–24 weeks),

adherent to liraglutide for >4 months and <6 months; and (4) ≥6 months (≥24 weeks), adherent to liraglutide treatment for ≥6 months.

Reasons for dropping out of liraglutide treatment were collected in the form of participant complaints recorded by physicians. They were classified into five categories: (1) unknown: the participants discontinued follow-up without any comment; (2) cost: the participants discontinued the treatment for financial reasons; (3) failure to lose weight: the participants failed to lose ≥5% of their baseline body weight within 12 weeks of treatment; (4) adverse events: the treatment was terminated due to local or systemic adverse events such as skin reactions at the injection site, nausea, vomiting, diarrhea, or any other gastrointestinal symptoms; and (5) the participants were switched to another anti-obesity treatment after consultation with their physician.

Statistical analysis

We performed analysis of variance for continuous numerical variables and Pearson's chi-square test for categorical variables to compare characteristics among the adherence groups. Linear-by-linear association tests for categorical variables and a general linear model for continuous variables were used to test for linear trends in the baseline characteristics and reasons for dropping out among the four groups. To identify significant factors affecting adherence to liraglutide treatment, a binomial multivariate logistic regression analysis using the forward stepwise selection method was performed using dropout before 6 months as the dependent variable and other factors (age, sex, height, weight, waist circumference, BMI quartile, systolic blood pressure, diastolic blood pressure, HbA1c, serum fasting glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, AST, ALT, BUN, creatinine, eGFR, presence of diabetes mellitus, presence of dyslipidemia, presence of hypertension, smoking status, regular exercise, treatment center, mean liraglutide dose, and initial weight change) as the independent variables. To derive associations between the adherence groups and the factors, a multinomial logistic regression was conducted based on the results of the binomial logistic regression analysis and adjusting for age, sex, BMI, dyslipidemia, hypertension, smoking status, treatment center, mean liraglutide dose, and initial weight change. All statistical analyses were performed using IBM SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA), and a *P*-value of <0.05 was considered to indicate statistical significance.

RESULTS

Baseline clinical characteristics of participants according to adherence groups

We enrolled 769 patients for the final analysis according to the eligibility criteria (n=63 in <2 months group, n=242 in 2–4 months group, n=234 in 4–6 months group, and n=230 in ≥6 months group). The mean follow-up durations were 3.9, 9.6, 17.8, and 29.9 weeks in the <2, 2–4, 4–6, and ≥6 month groups, respectively; the mean liraglutide dose in each group was 2.6, 2.1, 2.4, and 2.4 mg/day, respectively ($P<0.001$). The proportion of participants enrolled in each group from the seven centers of the obesity clinic was 77.8%, 40.9%, 35.9%, and 39.1%, respectively ($P<0.001$).

The overall mean age was found to increase significantly with the duration of each adherence group (41.2, 44.7, 44.5, and 46.6 years, respectively; $P=0.021$, P for trend=0.007). A similar trend was observed for waist circumference (98.1, 102.6, 104.7, and 105.5 cm, respectively; P for trend=0.04) and initial body weight change (–0.3%, –3.7%, –3.3%, and –4.5%, respectively; $P<0.001$, P for trend <0.001). Serum AST and creatinine levels exhibited a significantly increasing trend with adherence, whereas the HDL cholesterol level significantly decreased with increasing adherence (P for trend <0.05). The presence of diabetes mellitus and hypertension tended to increase with increasing adherence, and regular exercise tended to decrease with increasing adherence ($P<0.05$, P for trend <0.05). The remaining variables showed no significant differences or trends between the four groups (Table 1).

Reasons for dropping out of liraglutide treatment within 6 months

The reasons given by the 539 participants for discontinuing liraglutide treatment within 6 months are provided in Table 2. Remarkably, 90.5% of the participants in the <2 months group, 51.2% in the 2–4 months group, and 47.4% in the 4–6 months group were lost to follow-up for unknown reasons. Discontinuation due to cost was reported by 9.1% of the participants in the 2–4 months group and 9.0% of those in the 4–6 months group, whereas discontinua-

Table 1. Baseline clinical characteristics of study participants according to their adherence to liraglutide 3.0 mg treatment

Variable	Adherence group				*P**	*P* for trend
	<2 Months (n=63)	2–4 Months (n=242)	4–6 Months (n=234)	≥6 Months (n=230)		
Follow-up duration (wk)	3.9±1.5	9.6±2.4	17.8±2.6	29.9±6.5	<0.001	<0.001
Liraglutide dose (mg/dL)	2.6±0.7	2.1±0.8	2.4±0.7	2.4±0.7	<0.001	0.329
Obesity clinic†	49 (77.8)	99 (40.9)	84 (35.9)	90 (39.1)	<0.001	<0.001
Age (yr)	41.2±12.1	44.7±12.5	44.5±12.8	46.6±13.3	0.021	0.007
Sex					0.533	0.628
Male	23 (36.5)	69 (28.5)	76 (32.5)	77 (33.5)		
Female	40 (63.5)	173 (71.5)	158 (67.5)	153 (66.5)		
Height (cm)	164.7±10.0	163.9±8.3	165.3±9.6	164.4±9.4	0.422	0.630
Body weight (kg)	87.2±19.0	86.0±18.0	88.8±20.0	87.9±18.5	0.413	0.320
Waist circumference (cm)	100.0±9.6	102.2±9.8	104.6±12.7	105.2±10.1	0.212	0.040
BMI (kg/m^2)	31.9±4.5	31.9±5.4	32.3±5.1	32.3±4.8	0.769	0.342
BMI category (kg/m^2)					0.758	0.196
25.0–29.9	26 (41.3)	103 (42.6)	91 (38.9)	81 (35.2)		
30.0–34.9	25 (39.7)	94 (38.8)	87 (37.2)	99 (43.0)		
35.0–39.9	8 (12.7)	25 (10.3)	37 (15.8)	32 (13.9)		
≥40.0	4 (6.3)	20 (8.3)	19 (8.1)	18 (7.8)		
Initial weight change‡ (%)	–0.3±3.1	–3.7±3.8	–3.3±2.9	–4.5±4.8	<0.001	<0.001
Systolic BP (mmHg)	134.1±18.7	131.5±17.4	132.6±14.5	132.8±14.6	0.666	0.771
Diastolic BP (mmHg)	81.4±13.7	80.9±11.9	81.2±10.8	80.7±11.1	0.967	0.786
HbA1c (%)	7.3±1.9	6.7±1.6	6.6±1.5	6.9±1.5	0.272	0.460
Fasting serum glucose (mg/dL)	120.1±28.3	121.5±34.9	120.0±41.6	127.3±36.2	0.292	0.154
Total cholesterol (mg/dL)	183.5±27.6	183.5±41.6	183.4±42.4	178.8±41.3	0.693	0.316
Triglycerides (mg/dL)	193.0±146.1	166.1±97.3	172.4±105.5	182.8±100.6	0.409	0.383
HDL cholesterol (mg/dL)	48.3±10.8	50.4±12.0	49.2±12.3	47.2±10.7	0.108	0.044
LDL cholesterol (mg/dL)	106.7±31.6	114.5±35.8	117.0±34.8	110.8±31.4	0.288	0.739
AST (IU/L)	34.4±15.0	35.0±20.7	33.5±20.5	38.9±24.9	0.049	0.064
ALT (IU/L)	45.4±26.0	43.3±28.3	41.8±36.0	49.4±36.3	0.079	0.130
BUN (mg/dL)	13.2±4.0	13.7±4.1	14.4±7.2	15.0±6.5	0.316	0.060
Creatinine (mg/dL)	0.70±0.20	0.72±0.21	0.76±0.26	0.77±0.26	0.216	0.048
eGFR (mL/min/1.73 m^2)	110.1±29.0	103.8±2.8	102.8±19.9	101.8±21.1	0.359	0.141
Comorbidity						
Diabetes mellitus	10 (15.9)	79 (32.6)	83 (35.5)	114 (49.6)	<0.001	<0.001
Dyslipidemia	19 (30.2)	102 (42.1)	105 (44.9)	99 (43.0)	0.213	0.185
Hypertension	14 (22.2)	106 (43.8)	121 (51.7)	106 (46.1)	0.001	0.009
Smoking					0.585	0.269
Never	50 (79.4)	203 (83.9)	194 (82.9)	198 (86.1)		
Ex- or current smoker	13 (20.6)	29 (16.1)	40 (17.1)	32 (13.9)		
Regular exercise	21 (33.3)	61 (25.2)	71 (30.3)	29 (12.6)	<0.001	<0.001

Values are presented as mean±standard deviation or number (%). Adherence groups: ≥6 months, adherent to liraglutide treatment for >6 months; 4–6 months, adherent to liraglutide for >4 months and <6 months; 2–4 months, adherent to liraglutide for >2 months and <4 months; <2 months, lost to follow-up within 2 months of the index date.
*Analysis of variance for continuous variables and Pearson's chi-square test for discrete variables; †Participants enrolled from the seven centers of obesity clinics; ‡Weight change during the initial period (<2 months).
BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

tion due to weight loss failure was identified in 8.3% and 12.8% of the participants in the 2–4 and 4–6 months groups, respectively. Discontinuation due to adverse events was found in 3.2%, 17.4%, and 15.4% of the participants in the <2, 2–4, and 4–6 months groups, respectively. Participants who switched to another anti-obesity treatment constituted 6.3%, 14.0%, and 15.4% of the participants in the

Table 2. Reasons for dropping out of liraglutide 3.0 mg treatment within 6 months (n=539)

Reason	Adherence group			*P**	*P* for trend
	<2 Months (n=63)	2–4 Months (n=242)	4–6 Months (n=234)		
Unknown	57 (90.5)	124 (51.2)	111 (47.4)	<0.001	<0.001
Cost	0	22 (9.1)	21 (9.0)		
Failure to lose weight	0	20 (8.3)	30 (12.8)		
Adverse event	2 (3.2)	42 (17.4)	36 (15.4)		
Switch to another treatment	4 (6.3)	34 (14.0)	36 (15.4)		

Values are presented as number (%).
*Pearson's chi-square test.

Table 3. Factors affecting adherence to liraglutide 3.0 mg treatment for more than 6 months

Factor	Adjusted OR	95% CI	*P**
STEP 1			
Presence of diabetes mellitus	0.45	0.33–0.63	<0.001
STEP 2			
Presence of diabetes mellitus	0.48	0.35–0.66	<0.001
Regular exercise	2.35	1.52–3.64	<0.001

*Binomial logistic regression analysis using the forward stepwise selection method with dropout from liraglutide before 6 months as the dependent variable and age, sex (categorical), height, weight, waist circumference, body mass index quartile, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, serum fasting glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, estimated glomerular filtration rate, presence of diabetes mellitus (categorical), presence of dyslipidemia (categorical), presence of hypertension (categorical), smoking (categorical), regular exercise (categorical), treatment center (categorical), mean liraglutide dose, and initial weight change as independent variables.
OR, odds ratio; CI, confidence interval.

<2, 2–4, and 4–6 months groups, respectively ($P<0.001$, P for trend <0.001).

Factors affecting the adherence to liraglutide treatment for <6 months

To find factors that significantly affected the adherence to liraglutide treatment, we performed a binomial multivariate logistic regression analysis with the forward stepwise selection method, setting dropout before 6 months as the dependent variable and the other factors as independent variables. In step 1, the presence of diabetes mellitus was significantly associated with dropout before 6 months (odds ratio [OR], 0.45; 95% confidence interval [CI], 0.33–0.63). In step 2, regular exercise (OR, 0.48; 95% CI, 0.35–0.66) and the presence of diabetes mellitus (OR, 2.35; 95% CI, 1.52–3.64) differed significantly among the groups (Table 3).

Table 4. Association between the presence of diabetes mellitus or regular exercise and the risk of dropping out of liraglutide 3.0 mg treatment

Adherence group	Factor		Adjusted OR	95% CI	*P**
4–6 Months	Presence of diabetes mellitus	(–)	Ref		
		(+)	0.52	0.34–0.80	0.003
	Regular exercise	(–)	Ref		
		(+)	2.99	1.81–4.92	<0.001
2–4 Months	Presence of diabetes mellitus	(–)	Ref		
		(+)	0.47	0.31–0.73	0.001
	Regular exercise	(–)	Ref		
		(+)	2.09	1.26–3.48	0.004
<2 Months	Presence of diabetes mellitus	(–)	Ref		
		(+)	0.25	0.10–0.63	0.003
	Regular exercise	(–)	Ref		
		(+)	2.86	1.31–6.23	0.008

*Multinomial logistic regression analysis using the highest adherence group (≥6 months) as the reference value and adjusting for age, sex (categorical), body mass index quartile (categorical), presence of dyslipidemia (categorical), presence of hypertension (categorical), smoking status (categorical), treatment center (categorical), mean liraglutide dose, and initial weight change.
OR, odds ratio; CI, confidence interval.

Association between diabetes mellitus and exercise and the risk of dropping out of liraglutide treatment

Using the results of the binomial logistic regression analysis, we performed a multinomial logistic regression analysis to identify associations between adherence to liraglutide treatment and the presence of diabetes and regular exercise. After adjusting for covariates and using the group with longest adherence (≥6 months) as a reference, the OR for the presence of diabetes mellitus was 0.25 (95% CI, 0.10–0.63) in the <2 months group, 0.47 (95% CI, 0.31–0.73) in the 2–4 months group, and 0.52 (95% CI, 0.34–0.80) in the 4–6 months group; however, for regular exercise, the OR was 2.86 (95% CI, 1.31–6.23) in the <2 months group, 2.09 (95% CI, 1.26–3.48) in the 2–4 months group, and 2.99 (95% CI, 1.81–4.92) in the 4–6 months group (Table 4).

DISCUSSION

We performed a retrospective observational study to assess the adherence to liraglutide 3.0 mg for the obesity treatment in a real-world setting in South Korea. Overall, 60.3% of the patients ad-

hered to liraglutide 3.0 mg treatment for ≥4 months, and treatment adherence was better among patients who were older, had poor metabolic indices, had diabetes mellitus or hypertension, and did not exercise regularly. The multivariate analysis indicates that dropout was less likely to occur among patients with diabetes mellitus. In contrast, regular exercise was inversely related to the risk of dropout. These associations were consistent at all follow-up times (2, 4, and 6 months of liraglutide use).

Medication adherence is important in managing chronic diseases, and obesity is no exception. Generally, weight loss of 5%–10% of body weight within 6 months of beginning treatment is recommended for patients to obtain the desired health benefits;[3] in addition to weight loss, the long-term maintenance of weight loss is also important for achieving the desired health outcomes. The high dropout rate with anti-obesity drugs is a major barrier to achieving and sustaining weight loss and is closely related to weight cycling.[15] It varies widely depending on the type of drug[12] and is estimated to be 40%–50%.[16] Among the anti-obesity drugs, liraglutide is considered to have a lower risk of discontinuation than other drugs such as lorcaserin, naltrexone/bupropion, phentermine/topiramate, phentermine, and orlistat.[12,17]

In randomized controlled trials of liraglutide 3.0 mg, the dropout rate at 1 year ranged from 20% to 28% in the liraglutide groups, and the rate in the placebo groups was higher (26%–36%).[6,8,18,19] The dropout rate from liraglutide 3.0 mg treatment was 57.4% at 7 months in Switzerland,[20] approximately 46% at 6 months in Canada,[21] and 58.2% at 6 months in the United States.[17] In our Korean study, the dropout rate was 39.7% at 4 months and 70.1% at 6 months.

Possible reasons for the high dropout rate in Korea include the following. First, this study collected and analyzed data from the initial period of liraglutide availability in Korea. Before that period, orlistat, lorcaserin, and naltrexone/bupropion were available as oral anti-obesity drugs. Liraglutide was the only injectable, and it was the most expensive drug anti-obesity drug available. Prejudice against the injectable mode of administration and its high cost might underlie the low adherence rate reported here.[22] Interestingly, the participants who dropped out during early treatment disclosed no specific reasons for discontinuing their follow-up; however, those who dropped out after several months reported that they discontinued liraglutide 3.0 mg treatment for financial reasons or due to failure to lose weight. In this regard, physicians should consider patients' financial circumstances and their long-term preference for maintaining a lower weight. Second, the nine hospitals from which the data were collected are all tertiary hospitals; thus, the characteristics of participants in this study could differ from those of patients with obesity who visit primary clinics.[23] Third, obesity in the participants in this study was milder than in previous studies. In Korea, obesity is defined as a BMI of ≥25 kg/m^2; other countries use a BMI of ≥30 kg/m^2. Thus, the mean BMI of 32.1 kg/m^2 in this study is substantially lower than those reported in previous studies in Switzerland (36.2 kg/m^2) and Canada (32.9–46.3 kg/m^2). Nevertheless, although the participants in our study were leaner, they had more comorbidities than in previous studies, including diabetes mellitus,[20,21] which means that the less obese but metabolically unhealthier participants in our study were more likely than those in previous studies to be under polypharmacy, which could lead to poor adherence rates.[24]

Interestingly, regular exercise was significantly associated with lower adherence to liraglutide 3.0 mg treatment. Physical fitness and functional health status have been associated with non-adherence to medication in other chronic diseases, with a pooled prevalence of approximately 42.6%, and poorer health status is associated with a stronger motivation to continue medication.[25,26] Similar results showing a positive association between regular exercise and medication non-adherence have been found in Saudi Arabia and Japan.[27,28] On the other hand, exercise is an essential treatment for successful weight loss[3] and the main predictor of substantial weight loss.[29] Considering that adherence to a weight loss intervention usually correlates with adherence to physical activity,[30] patients who exercise regularly, have good adherence to healthy lifestyle guidelines, and make favorable behavioral changes might have high confidence that they can achieve weight loss without anti-obesity medication.

Patients with diabetes had better than average adherence to liraglutide 3.0 mg treatment in our study, indicating that diabetes mellitus also significantly affects adherence. Liraglutide is a highly efficient, glucose-lowering GLP-1 RA that can be used to treat both diabetes mellitus and obesity.[31] Patients with both conditions are likely to adhere to GLP-1 RA therapy better than diabetes patients without obesity,[32] and patients with diabetes mellitus who achieved

substantial weight loss had significantly better adherence to medication and other treatment regimens than those with weight gain.[33,34] Therefore, it is not surprising that patients with both obesity and diabetes who achieved weight loss in our study displayed better than average adherence. For such patients, treatment using GLP-1 RAs such as liraglutide 3.0 mg are a viable option for achieving both weight loss and glycemic control.

This study has certain limitations. First, the high dropout rate and limited data availability could lead to attrition bias because of the possibility of other confounding variables. Second, as mentioned before, the population in this study was enrolled from tertiary hospitals. Because the medical expenses associated with tertiary hospitals are higher than those with primary clinics, the characteristics of the participants in this study could vary from those of patients in primary clinics. Therefore, the possibility of selection bias cannot be ruled out. Third, because this study was conducted in a single country, the results cannot be generalized to other ethnic groups.

Despite those limitations, this study has several strengths. It is the first study to use representative real-world data from multiple institutions and regions of South Korea to investigate the adherence to and causes of dropout from treatment with liraglutide. The use of multi-level statistical analyses with various covariates is another strength.

In conclusion, the dropout rate for liraglutide 3.0 mg treatment was relatively high in a real-world setting in South Korea. Of note, among the people with obesity, individuals who exercised regularly and those without diabetes mellitus were likely to have poor adherence to liraglutide treatment. Further studies are needed to investigate how to increase drug adherence to liraglutide 3.0 mg to achieve and maintain weight loss in those patients.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: HJK and SL; acquisition of data: HJK, JWK, and SL; analysis and interpretation of data: HJK; drafting of the manuscript: HJK and JWK; critical revision of the manuscript: SL; statistical analysis: HJK; administrative, technical, or material support: SL; and study supervision: SL.

REFERENCES

1. World Health Organization. Obesity and overweight [Internet]. Geneva: World Health Organization; 2021 [cited 2022 Aug 17]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Nam GE, Kim YH, Han K, Jung JH, Rhee EJ, Lee WY, et al. Obesity fact sheet in Korea, 2020: prevalence of obesity by obesity class from 2009 to 2018. J Obes Metab Syndr 2021; 30:141-8.
3. Kim BY, Kang SM, Kang JH, Kang SY, Kim KK, Kim KB, et al. 2020 Korean Society for the Study of Obesity guidelines for the management of obesity in Korea. J Obes Metab Syndr 2021;30:81-92.
4. Larsen JR, Vedtofte L, Jakobsen MS, Jespersen HR, Jakobsen MI, Svensson CK, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. JAMA Psychiatry 2017;74:719-28.
5. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DC, Van Gaal L, et al. 3 Years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399-409.
6. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes Randomized Clinical Trial. JAMA 2015;314:687-99.
7. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond) 2016;40:1310-9.
8. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373: 11-22.

9. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
10. Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, et al. Medication adherence: a call for action. Am Heart J 2011;162:412-24.
11. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. MedGenMed 2007;9:58.
12. Ahmad NN, Robinson S, Kennedy-Martin T, Poon JL, Kan H. Clinical outcomes associated with anti-obesity medications in real-world practice: a systematic literature review. Obes Rev 2021;22:e13326.
13. Park JH, Kim JY, Choi JH, Park HS, Shin HY, Lee JM, et al. Effectiveness of liraglutide 3 mg for the treatment of obesity in a real-world setting without intensive lifestyle intervention. Int J Obes (Lond) 2021;45:776-86.
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
15. DerSarkissian M, Bhak RH, Huang J, Buchs S, Vekeman F, Smolarz BG, et al. Maintenance of weight loss or stability in subjects with obesity: a retrospective longitudinal analysis of a real-world population. Curr Med Res Opin 2017;33:1105-10.
16. Daubresse M, Alexander GC. The uphill battle facing antiobesity drugs. Int J Obes (Lond) 2015;39:377-8.
17. Ganguly R, Tian Y, Kong SX, Hersloev M, Hobbs T, Smolarz BG, et al. Persistence of newer anti-obesity medications in a real-world setting. Diabetes Res Clin Pract 2018;143:348-56.
18. Wadden TA, Tronieri JS, Sugimoto D, Lund MT, Auerbach P, Jensen C, et al. Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: the SCALE IBT Randomized Controlled Trial. Obesity (Silver Spring) 2020;28:529-36.
19. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013;37:1443-51.
20. Haase CL, Serratore Achenbach MG, Lucrezi G, Jeswani N, Maurer S, Egermann U. Use of liraglutide 3.0 mg for weight management in a real-world setting in Switzerland. Obes Facts 2021;14:568-76.
21. Wharton S, Haase CL, Kamran E, Liu A, Mancini J, Neish D, et al. Weight loss and persistence with liraglutide 3.0 mg by obesity class in the real-world effectiveness study in Canada. Obes Sci Pract 2020;6:439-44.
22. Matza LS, Curtis SE, Jordan JB, Adetunji O, Martin SA, Boye KS. Physician perceptions of GLP-1 receptor agonists in the UK. Curr Med Res Opin 2016;32:857-64.
23. Kim AM, Cho S, Kim HJ, Jung H, Jo MW, Lee JY, et al. Primary care patients' preference for hospitals over clinics in Korea. Int J Environ Res Public Health 2018;15:1119.
24. Muth C, Blom JW, Smith SM, Johnell K, Gonzalez-Gonzalez AI, Nguyen TS, et al. Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus. J Intern Med 2019;285:272-88.
25. Foley L, Larkin J, Lombard-Vance R, Murphy AW, Hynes L, Galvin E, et al. Prevalence and predictors of medication nonadherence among people living with multimorbidity: a systematic review and meta-analysis. BMJ Open 2021;11:e044987.
26. Warner LM, Schüz B, Aiken L, Ziegelmann JP, Wurm S, Tesch-Römer C, et al. Interactive effects of social support and social conflict on medication adherence in multimorbid older adults. Soc Sci Med 2013;87:23-30.
27. Altamimi AF, Alqahtani ZA, Almughaiseeb FA, Alshiha KA, Alaryni A, Alotaibi A. The attitude and prevalence of patient noncompliance toward chronic disease medications in Saudi Arabia. J Family Med Prim Care 2021;10:3064-70.
28. Nakajima R, Watanabe F, Kamei M. Factors associated with medication non-adherence among patients with lifestyle-related non-communicable diseases. Pharmacy (Basel) 2021;9:90.
29. Byrne S, Barry D, Petry NM. Predictors of weight loss success: exercise vs. dietary self-efficacy and treatment attendance. Appetite 2012;58:695-8.
30. Tronieri JS, Fabricatore AN, Wadden TA, Auerbach P, Endahl L, Sugimoto D, et al. Effects of dietary self-monitoring, physical activity, liraglutide 3.0 mg, and placebo on weight loss in the SCALE IBT Trial. Obes Facts 2020;13:572-83.

31. Iepsen EW, Torekov SS, Holst JJ. Liraglutide for type 2 diabetes and obesity: a 2015 update. Expert Rev Cardiovasc Ther 2015;13:753-67.
32. Weiss T, Yang L, Carr RD, Pal S, Sawhney B, Boggs R, et al. Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK. BMJ Open Diabetes Res Care 2022;10:e002517.
33. Grandy S, Fox KM, Hardy E; SHIELD Study Group. Association of weight loss and medication adherence among adults with type 2 diabetes mellitus: SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes). Curr Ther Res Clin Exp 2013;75:77-82.
34. Boye KS, Shinde S, Kennedy-Martin T, Robinson S, Thieu VT. Weight change and the association with adherence and persistence to diabetes therapy: a narrative review. Patient Prefer Adherence 2022;16:23-39.