VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

Haider Ayad Alidrisi[1], Sameh Abed Odhaib[2], Hussein Ali Nwayyir[1], Ammar Mohammed Saeed Almomin[3]

[1]Faiha Specialized Diabetes, Endocrine, and Metabolism Center, University of Basrah College of Medicine, Basrah, Iraq
[2]Thi-Qar Specialized Diabetes, Endocrine and Metabolism Center, Thi-Qar, Iraq
[3]Faiha Specialized Diabetes, Endocrine, and Metabolism Center, Basrah Health Directorate, Basrah, Iraq

Effectiveness and Safety of Add-on Once-Daily Liraglutide (1.2 mg) in Type 2 Diabetes Patients with Obesity: Data from a Real-World Cohort of Iraqi Patients

ABSTRACT

Objective: This study aimed to evaluate real-world effectiveness and safety of once-daily liraglutide (1.2 mg) as an add-on to oral antidiabetic drugs (OADs) and/or insulin, in type 2 diabetes (T2D) patients with obesity in Iraq.

Materials and methods: A total of 55 T2D patients with obesity (mean ± SD age: 46.5 ± 8.7 years, 60% were females) initiating once-daily liraglutide (1.2 mg) as an add-on to OADs and/or insulin were included in this prospective cohort study. Change in body weight and serum HbA1c levels, and the insulin and sulfonylurea (SU) requirement were recorded during 24-week liraglutide therapy.

Results: Liraglutide yielded significant reduction in HbA1c values (from 10.7 ± 2.0% at baseline to 8.7 ± ± 2.4 % and 8.1 ± 1.6 % at weeks 12 and 24, respectively, $p < 0.001$ for each) and body weight (from 112.0 ± 19.6 kg at baseline to 109 ± 19.1 kg, 102 ± ± 16.9 kg and 97.0 ± 15.8 kg at weeks 4, 12 and 24, respectively, $p < 0.001$ for each). SU was stopped in 9/17 (52.9%) patients, and insulin therapy was discontinued in 15/44 (34%) patients after liraglutide treatment, and either with discontinuation or switch to basal insulin, 22/34 (64.7%) patients were no longer requiring prandial insulin (premixed and basal/bolus). No unexpected safety or tolerability issues occurred.

Conclusions: In conclusion, our findings support the consideration of liraglutide as a favorable intensifying therapy in T2D patients with obesity and metformin failure, given that it enables a sustained HbA1c and body weight reduction even at 1.2 mg once-daily dose, alongside the potential benefits in reducing SU and insulin requirements with no serious side effects.

Keywords: type 2 diabetes, obesity, liraglutide 1.2 mg daily dose, efficacy, real-world, Iraq

Address for correspondence:
Haider Ayad Alidrisi MD, FIBMS, CABM, MSc Endocrinology, FACE
Faiha Specialized Diabetes, Endocrine, and Metabolism Center, University of Basrah, College of Medicine, Basrah, Iraq
Phone: +9647705021502
E-mail: haider.alidrisi@fdemc.iq; haider.alidrisi@uobasrah.edu.iq
Clinical Diabetology
DOI: 10.5603/cd.99656
Received: 5.03.2024 Accepted: 28.03.2024
Early publication date: 22.04.2024

Introduction

Obesity is a strong risk factor and a frequent comorbidity of type 2 diabetes (T2D), with presence of overweight or obesity in up to 85.2% of T2D patients at the time of diagnosis [1, 2]. Both obesity and T2D are associated with high susceptibility to diseases as-

sociated with increased risk of premature mortality, and thus weight reduction has clinically meaningful implications in T2D [2–4].

Also, the avoidance of hypoglycemia and weight gain are amongst the key considerations in selecting the appropriate individualized treatment intensification following failure of first line therapy [5, 6]. Liraglutide (Victoza®), once-daily glucagon-like peptide-1 (GLP-1) analog used at doses 1.2 to 3.0 mg, is considered a preferable noninsulin injectable agent following metformin, given its potential to enable optimal care via patient-oriented treatment goals (i.e., lower risk of weight gain, hypoglycemia and cardiovascular complications) beyond the improved glycated hemoglobin (HbA1c) values [5–8].

Observational real-world studies are considered to be of utmost importance to ascertain the long-term impacts of liraglutide in diverse patient populations and clinical settings and to explore the factors having a high impact on liraglutide-mediated effects [9, 10]. The real-world data on the effect of liraglutide in obese people with T2D as well as in those using injectable therapy are scarce in Iraq.

Therefore, this study aimed to evaluate the effectiveness (HbA1c and weight reduction) and safety of once-daily liraglutide (1.2 mg; less expensive dose), as an add-on to OADs and/or insulin, in a real-world cohort of Iraqi T2D patients with obesity. The additional objectives were to determine the baseline patient/clinical characteristics with a potential for better liraglutide effectiveness, and to evaluate the changes in insulin and SU requirement during the liraglutide treatment.

Materials and methods

Study population

A total of 55 T2D patients with obesity (mean ± SD age: 46.5 ± 8.7 years, 60% were females) initiating liraglutide as an add-on to OADs and/or insulin were included in this prospective cohort study conducted at two tertiary care specialized diabetes centers in Iraq. Adult patients (16–65 years of age) with T2D who failed to achieve glycemic control (HbA1c > 7%) and weight reduction (body mass index [BMI] ≥ 30 kg/m^2) on OADs and/or insulin and gave consent to initiate liraglutide and pay for it were included in the study. Previous history of bariatric surgery or intervention, previous weight-loss treatment, personal and/or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 and pregnancy were the exclusion criteria of the study.

Verbal consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Faiha Specialized Diabetes Endocrine and Metabolism Center (FDEMC) Research (date of approval: 1/05/2021; protocol no: 66/31/21).

Assessments

Data on patient demographics, duration of diabetes, ongoing anti-diabetic treatment (OADs, insulin) and cardiovascular disease history were recorded at baseline. Data on body weight (kg) and serum HbA1c (%) levels were recorded at baseline and during 24-week liraglutide therapy (at weeks 4,12 and 24 for the body weight, and at weeks 12 and 24 for the HbA1c). Changes in the insulin and SU requirements depending on the self-monitoring blood glucose (SBGM) recordings were evaluated during 4th, 12th and 24th weeks of liraglutide therapy. Treatment-related adverse events were recorded at 1st, 4th, 12th and 24th weeks of liraglutide therapy. The changes in HbA1c and body weight under 24-week liraglutide therapy was also evaluated in subgroups of age (< 50 years vs. ≥ 50 years), gender (male vs. female), diabetes duration (< 5 years vs. ≥ 5 years) and concomitant insulin treatment (yes vs. no).

Liraglutide treatment

Patients received once-daily subcutaneous liraglutide (Victoza®) therapy at a starting dose of 0.6 mg/day for one week, which was then titrated up to 1.2 mg/day for 24 weeks.

SMBG recordings

Each patient was instructed to do a 4–6-point SMBG before and after each meal at home through the period of the study. The SMBG data on fasting blood glucose (FBG), pre-meal blood glucose (BG), and 2-hour postprandial blood glucose (PPG) were evaluated at 1st, 4th, 12th and 24th weeks of therapy.

Modification of anti-diabetes treatments

All patients received 2 g metformin per day in addition to standard life-style interventions (diet and exercise). For other OADs and insulin therapy, treatment modifications were based on FBG, 2h PPG or pre-meal BG levels obtained through analysis of SMBG data.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Change over time was analyzed with dependent group t test or Wilcoxon test depending on the distribution pattern of continuous variables.

Repeated-measures analysis of variance (ANOVA) with a Greenhouse-Geisser correction and post hoc test with Bonferroni correction were used to compare the mean reductions in HbA1c and body weight at the points of evaluations after liraglutide initiation. Data were expressed as mean ± standard deviation (SD) and percent (%) where appropriate. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and anti-diabetic treatments

Mean ± SD age was 46.5 ± 8.7 years, and females comprised 60.0% of the study population. Mean ± SD duration of diabetes was 6.3 ± 3.4 years (≥ 5 years in 67.3%). Mean ± SD body weight, BMI and HbA1c values at baseline were 112.0 ± 19.6 kg, 41.2 ± 7.4 kg/m^2 and 10.7 ± 2.0%, respectively (Tab. 1).

Prior to add-on liraglutide therapy, 80% of patients were receiving insulin (premixed insulin in 36.4%) and 78.2% were on metformin therapy. SU, DPP4i and pioglitazone were the other antidiabetic treatments in 30.9%, 21.8% and 9.1% of patients, respectively (Tab. 1).

Table 1. Baseline Characteristics and Anti-Diabetic Treatments

Patient demographics	
Age [year], mean ± SD	46.5 ± 8.7
Gender (F), n (%)	33 (60.0)
Duration of diabetes [year], mean ± SD	6.3 ± 3.4
≥ 5 years of duration, n (%)	37 (67.3)
Cardiovascular disease history, n (%)	8 (14.5)
Baseline measurements, mean ± SD	
Weight [kg]	112.0 ± 19.6
BMI [kg/m2]	41.2 ± 7.4
HbA1c [%]	10.7 ± 2.0
Anti-diabetic treatments, n (%)	
OADs	
Metformin	43 (78.2)
SU	17 (30.9)
DPP4i	12 (21.8)
Pioglitazone	5 (9.1)
Insulin	44 (80.0)
Basal insulin	10 (18.2)
Premixed insulin	20 (36.4)
Basal/bolus insulin	14 (25.4)

BMI — body mass index; DPP4i — dipeptidyl peptidase-4 inhibitor; HbA1c — glycated hemoglobin; OADs — oral antidiabetics; SU — sulfonylurea

HbA1c reduction after add-on liraglutide therapy

When compared to baseline HbA1c values (10.7 ± ± 2.0%), 12th week (8.7 ± 2.4 %, $p < 0.001$) and 24th week (8.1 ± 1.6 %, $p < 0.001$) assessments revealed significant improvement in HbA1c levels. There was also significant reduction in HBA1c values from the 12th week to 24th week of therapy ($p = 0.007$) (Fig. 1).

At weeks 12 and 24, the absolute changes from the baseline HbA1c were –1.9 ± 1.5% and –2.6 ± 1.5%, while the percent changes from baseline were 18.9 ± ± 12.5% and 23.3 ± 11.0%, respectively.

Weight reduction after add-on liraglutide therapy

When compared to baseline values (112.0 ± ± 19.6 kg), body weight was significantly reduced at 4th week (109 ± 19.1 kg, $p < 0.001$), 12th week (102 ± ± 16.9 kg, $p < 0.001$) and 24th week (97.0 ± 15.8 kg, $p < 0.001$) of therapy. There was also significant reduction in body weight throughout the follow up visits ($p < 0.001$ for each) (Fig. 1).

At weeks 4, 12 and 24, the absolute changes from the baseline weight were –3.0 ± 2.5 kg, –9.7 ± 7.3 kg, and –14.5 ± 9.7 kg, while the percent changes from baseline were 2.7 ± 1.9%, 8.4 ± 4.9%, and 12.5 ± ± 6.7%, respectively.

HbA1c and body weight reduction in subgroups

The significant reduction in HbA1c and body weight values were consistent throughout the follow up visits, regardless of the age, gender, diabetes duration, and concomitant insulin therapy ($p < 0.001$ for each) (Tab. 2).

Nonetheless, mean ± SD HbA1c reduction at 12th week was greater in patients with shorter (< 5 years) vs. longer (≥ 5 years) disease duration (2.7 ± 2.0 vs. 1.6 ± 1.0%, $p = 0.01$), and in non-insulin-treated vs. insulin-treated patients (2.6 ± 1.7 vs. 1.4 ± 0.9%, $p = 0.04$). Also, mean ± SD body weight reduction at 12th week was greater in patients <50 years of age vs. those ≥ 50 years of age (10.0 ± 7.9 vs. 9.2 ± 6.0 kg, $p = 0.03$), in males vs. females (11.7 ± 9.5 vs. 8.3 ± ± 5.0 kg, $p = 0.01$), and in non-insulin-treated patients vs. insulin-treated patients (11.9 ± 9.8 vs. 7.7 ± 2.8 kg, $p = 0.03$) (Tab. 2).

Changes in the insulin and SU requirement

At 12 weeks of liraglutide treatment, SU was stopped in 9 (52.9%) out of 17 SU-treated patients and basal insulin was stopped in 7 (70.0%) of 10 patients on basal insulin therapy. Of 20 patients on premixed

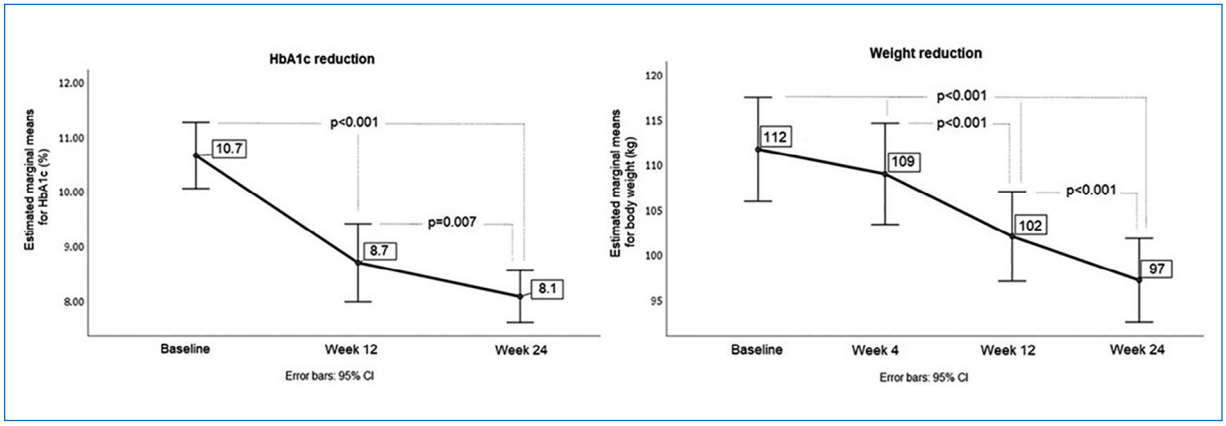

Figure 1. HbA1c reduction at Week 12 and Week 24 of Therapy and Weight Reduction at Week 4, Week 12 and Week 24 of Therapy
CI — confidence interval; HbA1c — glycated hemoglobin

Table 2. HbA1c and Body Weight Reduction in Subgroups of Age, Gender, Disease Duration and Insulin Therapy

Subgroups		Reduction in HbA1c [%], mean ± SD			
		12 weeks	24 weeks	p-value	
				Intra-group	Inter-group
Age	< 50 years	1.8 ± 1.6	2.6 ± 1.6	< 0.001	0.06
	≥ 50 years	2.2 ± 1.2	2.4 ± 1.0	< 0.001	
Gender	Male	2.1 ± 1.8	3.4 ± 1.5	< 0.001	0.05
	Female	1.8 ± 1.2	2.0 ± 1.1	< 0.001	
Diabetes duration	< 5 years	2.7 ± 2.0	2.4 ± 1.7	< 0.001	0.01
	≥ 5 years	1.6 ± 1.0	2.6 ± 1.4	< 0.001	
Insulin therapy	Yes	1.4 ± 0.9	2.5 ± 1.4	< 0.001	0.04
	No	2.6 ± 1.7	2.5 ± 1.6	< 0.001	

Subgroups		Reduction in body weight [kg], mean ± SD				
		Week 4	Week 12	Week 24	p-value	
					Intra-group	Inter-group
Age	< 50 years	2.9 ± 2.2	10.0 ± 7.9	15.8 ± 10.5	< 0.001	0.03
	≥ 50 years	3.3 ± 3.1	9.2 ± 6.0	11.5 ± 6.8	< 0.001	
Gender	Male	2.9 ± 2.1	11.7 ± 9.5	19.9 ± 11.7	< 0.001	0.01
	Female	3.1 ± 2.7	8.3 ± 5.0	10.0 ± 5.9	< 0.001	
Diabetes duration	< 5 years	4.5 ± 3.3	12.4 ± 11.1	16.1 ± 13.4	0.001	0.2
	≥ 5 years	2.3 ± 1.6	8.4 ± 3.9	13.8 ± 7.5	< 0.001	
Insulin therapy[a]	Yes	1.7 ± 1.1	7.7 ± 2.8	12.7 ± 5.9	< 0.001	0.03
	No	4.4 ± 2.8	11.9 ± 9.8	16.8 ± 12.8	< 0.001	

[a]Those continued insulin after 12 weeks of liraglutide initiation, whether on the same or a reduced dosage regimen

HbA1c — glycated hemoglobin; SD — standard deviation

insulin, 6 (30.0%) patients stopped insulin and further 6 (30.0%) were switched to basal insulin. Of 14 patients on basal/bolus insulin, 2 (14.3%) stopped insulin and 8 (57.1%) were switched to basal insulin. Overall, insulin therapy was discontinued in 15/44 (34%) patients after liraglutide treatment, and either with discontinuation or switch to basal insulin, 22/34 (64.7%) patients were no longer requiring prandial insulin (premixed and basal/bolus) (Fig. 2).

Treatment-related adverse events

The most frequently reported adverse events were nausea [by 36 (65.5%) and 19 (34.5%) patients at weeks 1 and 4, respectively] and vomiting [by 14

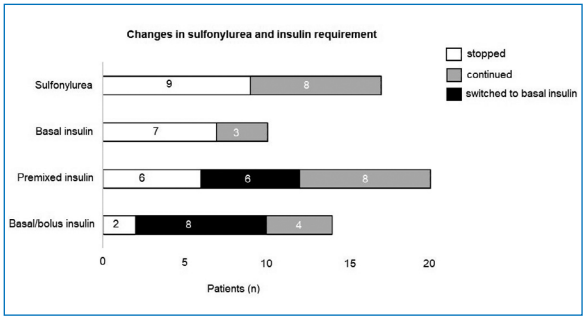

Figure 2. Changes in the Insulin and Sulfonylurea Requirement with Liraglutide Treatment

(25.5%) and 4 (7.3%) patients at weeks 1 and 4, respectively], which were gradually decreased towards the 4th week of therapy, and reported by none of the patients at 12th and 24th weeks. Hypoglycemia (SMBG < 70 mg/dL with or without symptoms) was reported by 2 (3.6%) and 6 (10.9%) insulin-treated patients at weeks 1 and 4, respectively, while no hypoglycemic events occurred at 12th and 24th weeks of therapy. No serious side effects were reported like acute pancreatitis or cholelithiasis.

Discussion

The present real-world cohort of T2D patients with obesity (mean age: 46.5 years, 60.0% were females, 67.3% with > 5 years of diabetes duration, 78.2% on metformin and 80.0% on insulin) indicated that the use of liraglutide in routine clinical practice, even at the lowest effective once-daily dose of 1.2 mg, successfully promoted the reduction of HbA1c values and significant weight loss, which was maintained throughout the study. The decrease in SU and insulin need was remarkable, which were no longer required by 52.9% and 34.0% of patients after 12th week of liraglutide therapy, respectively. Notably, liraglutide abolished the prandial insulin (premixed and basal/bolus) need in 64.7% patients through discontinuation or switch to basal insulin.

Similarly, in another study among Iraqi T2D patients with obesity (mean age: 48 years, 51.9% were males, diabetes duration < 5 years in 51.9%), a 1.2 mg daily dose of liraglutide as an add-on to OADs was reported to be associated with weight loss by 8.0% (–9.1 kg on average) and HbA1c reduction by 20% (–2.0% on average) at the end of 12th week [11]. Also, the higher liraglutide doses (1.8 mg/day) were associated with greater reduction in HbA1c (by 26.5%, –2.6% on average) levels, whereas no further reduction in body weight was noted with increasing the dosage from 1.2 to 1.8 mg/day (by 11.9%, –13.6 kg on average) [11].

In a prospective observational study in an Arab population of T2D patients (mean age 50.4 years, 71% were females, 56.3% were on insulin-based regimen, 90.1% were on metformin), 1.2 to 1.8 mg once-daily dose of liraglutide revealed a reduction in HbA1c from 8.3% to 7.7% at the 3rd month and to 7.6% at the 6th month, along with weight reduction of –2.01 ± 0.3 kg and –2.5 ± 0.6 kg, respectively [12].

In a real-world Portuguese cohort of T2D patients with obesity (median age: 59 years, 60.7% were females, 98.4% were under anti-diabetic), liraglutide effectively reduced HbA1c levels from 8.3% to 7.5%, while a weight reduction of at least 3% was noted in 44.0%, 47.6%, and 54.4% of patients at 6, 12, and 24 months, respectively [9].

In another real-world study ofT2D patients with obesity in Saudi Arabia (mean age: 54.9 years, 60.3% were females, concomitant insulin in 77.3%, metformin in 80.2%), liraglutide was associated with significantly reduced HbA1c (–0.9% on average) and weight loss (–2.3 kg on average) [13]. Also, the covariates (age, gender, insulin use) had no significant impact on HbA1c and weight, while higher baseline HbA1c (> 9%) and weight (>100 kg) were associated with greater improvements [13].

In a systematic review of 106 studies on the effectiveness of liraglutide in the real-world setting of T2D, the mean HbA1c change from baseline was reported range from –0.6% to –2.26%, while the mean weight from baseline ranged from –1.3 kg to –8.65 kg [14].

The LEAD trial program revealed 1.2–1.6% reduction in HbA1c and 1.8 to 3.2 kg reduction in body weight at liraglutide doses of 1.2–1.8 mg [15]. In the SUSTAIN 10 trial, once-daily 30-week liraglutide (1.2 mg) in patients with T2D uncontrolled by 1–3 OADs was reported to reduce mean HbA1c (baseline 8.2%) by 1.0% and mean body weight (baseline 96.9 kg) by 1.9 kg [16].

In a meta-analysis of 9 RCTs including 2981 patients receiving liraglutide as an add-on to metformin, the authors reported significant reduction in HbA1c values at 1.8 mg/day (by –0.47%) and 1.2 mg/day (by –0.35%) doses of liraglutide [17].

Accordingly, despite use of lowest effective dose, the HbA1c reduction and weight loss obtained via liraglutide treatment in our patients seem to be higher than those reported by other liraglutide studies in T2D patients including clinical trials [15–17] as well as most real-world studies [9, 12–14]. This may relate to the fact that the insulin and SU treatments were no longer required by a considerable proportion of our patients after the 12-week of liraglutide therapy, both of which

are known to be associated with weight gain (4 kg with insulin and 2 kg with SUs) [18].

In the present study, more advantageous groups in terms of better liraglutide effectiveness were those with < 5 years of diabetes duration and insulin-naïve status for a greater HbA1c reduction, and those with < 50 years of age, male gender and insulin-naïve status for a greater weight loss. Similarly, a higher baseline HbA1c, longer duration of T2D, and concomitant insulin and longer duration of insulin treatment have been shown to counter the glycemic effects of liraglutide, while weight reduction was correlated positively with a higher baseline weight and a longer duration of liraglutide treatment, and negatively with the prior insulin treatment [10].

The LEAD series of studies revealed inconsistent data on the correlates of weight loss caused by liraglutide treatment, which was found to be dose-dependent in LEAD-2 and LEAD-4, to be closely related to nausea and not dose-dependent in LEAD-3, and to be independent of gastrointestinal adverse reactions in LEAD-5, although a few patients with sustained nausea seemed to lose more weight [19–21].

In our cohort, insulin therapy was stopped by one third of liraglutide-treated patients, and either via discontinuation or switch to basal insulin, two third of patients were no longer requiring prandial insulin (premixed and basal/bolus). In this regard, the decrease in insulin need in our patients seems to be consistent with the post-prandial effects of GLP-1 RAs (through decelerating gastric emptying, stimulating insulin, or suppressing glucagon secretion), which enables to achieve the target ranges for fasting, post-prandial, and overall (HbA1c) glycemic control [22, 23].

Notably, basal insulin when combined with liraglutide is considered to result in clinically significant weight loss relative to treatment with insulin alone, which is the rationale behind the fixed-ratio combination of insulin degludec/liraglutide (IDegLira) studies [24–26].

The SCALE Diabetes trial in 846 T2D patients with overweight or obesity from 9 countries compared the 56-week use of once-daily 3.0 mg liraglutide (n = 423), 1.8 mg liraglutide (n = 211) and placebo (n = 212) as an add-on therapy to 0–3 OADs (metformin, thiazolidinedione, SU) [7]. The significantly higher weight loss was noted with 3.0 mg liraglutide (6.0%, 6.4 kg) than with 1.8 mg liraglutide (4.7%, 5.0 kg) or placebo (2.0%, 2.2 kg) [7]. The SCALE Insulin trial which included T2D patients with overweight or obesity treated with basal insulin and ≤ 2 OADs, revealed that at 56 weeks, liraglutide 3.0 mg (n = 198) was associated with a mean weight change of –5.8% (versus –1.5% with placebo) and a ≥ 5% weight loss in 51.8% of patients (vs. 24.0% with placebo), in addition to less need for insulin and significantly greater reductions in mean HbA1c despite lower basal insulin requirements [25]. These glycemic improvements are considered likely the result of the preferential effects of liraglutide on post-prandial (rather than pre-prandial) glucose combined with the significantly greater weight loss versus placebo [25]. Notably, the weight loss findings in the SCALE Insulin trial are in line with those observed in the previously described SCALE Diabetes trial in which insulin-treated individuals were excluded [7, 25].

In our cohort, despite presence of younger patients but higher baseline body weight as compared to the SCALE Insulin trial, once-daily liraglutide (1.2 mg) achieved 12.5% weight loss after 24 weeks. Besides, younger age was found to be associated with better liraglutide-mediated weight reduction, which seems notable given that younger age groups of diabetes patients are considered to have a lower adherence to a diabetes care plan and lifestyle changes due to the active occupational and social life in this age group [11]. In fact, patient adherence is considered the key factor determining the treatment effectiveness, specifically, in the real-world studies [24], while being accustomed to treatment with injectable insulins is considered likely to have a positive influence on treatment adherence to liraglutide in insulin-treated patients [25].

Hence, the association of younger age particularly with the improved weight loss outcome in our patients may indicate the likelihood of obesity rather than the early-stage diabetes to be considered bothersome and a major complaint by younger patients, leading to the adoption of a better self-care practice towards improved adherence to lifestyle interventions.

Nonetheless, whether the weight loss observed in our study is the result of the direct (via feelings of hunger and satiety and delayed gastric emptying) or indirect (reduced insulin and SU requirements) action of liraglutide requires further investigation, in addition to potential role of improved patient adherence [25].

Hence, our findings support the use of liraglutide for treatment intensification in T2D patients with obesity, even before insulin treatment, as a preferred noninsulin injectable agent providing effective HbA1c reduction and the additional benefit of weight loss and no intrinsic risk of hypoglycemic episodes [5, 6, 8, 11]. Similarly, the LIRA PRIME study in the primary care setting suggested that treatment intensification with liraglutide as add on therapy to metformin OADs is a feasible and effective strategy in patients with metformin-failure, given that liraglutide was associated with similar rates of hypoglycemia but a greater

HbA1c and body weight reductions versus a pooled OAD group (SGLT 2i, DPP 4i, and SUs) [27].

Notably, liraglutide is suggested to show higher efficacy when used as an add-on to metformin alone than when used as an add-on to insulin secretagogues, particularly in reducing cardiovascular risk in T2D patients [28]. In fact, use of liraglutide as add-on treatment (versus switching to liraglutide), and using liraglutide 1.2 mg (versus the highest dose of 1.8 mg) were considered amongst the positive predictors of achieving an HbA1c reduction of ≥ 1%, together with higher baseline HbA1c, shorter diabetes duration (versus > 5 years) and prior metformin monotherapy [29].

Safety data in our patients support the consistently reported favorable tolerability profile of liraglutide in T2D patients, including relatively frequent (but moderate and transient) gastrointestinal adverse events (i.e., nausea and vomiting and diarrhea) during first weeks of therapy, while the major hypoglycemic episodes are also considered to be uncommon, possibly due to liraglutide's glucose-dependent mechanism of action [9, 13–15, 19, 21, 27, 30].

The major strength of our study seems to be the detailed analysis of the effectiveness of the lowest effective dose of liraglutide, with consideration of potential confounders and the changes in insulin and SU requirement, in a real-world cohort of Iraqi T2D outpatients with obesity. However, there are also a few limitations that should be considered, such as the small sample size and the potential presence of selection bias and uncontrolled variables due to observational non-controlled and non-randomized design, as well as the lack of data on certain patient-reported outcome measures related to quality of life or treatment satisfaction.

Conclusions

In conclusion, our findings revealed that once-daily liraglutide (1.2 mg) as an add-on to OAD and/or insulin therapy significantly improved HbA1c levels and enabled weight loss, along with a favorable safety profile and decreased insulin and SU need, among Iraqi T2D patients with obesity. The HbA1c reduction and weight loss were both maintained throughout the 24-week treatment period and more pronounced in non-insulin treated patients, while the liraglutide therapy also reduced the need for SUs and insulin. Accordingly, our findings support the consideration of liraglutide as a favorable intensifying therapy in T2D patients with obesity and metformin failure, given that it enables a sustained HbA1c and body weight reduction even at 1.2 mg once-daily dose, alongside the potential benefits in reducing SU and insulin requirements with no serious side effects.

Article information

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request

Ethics statement

This study was approved by the Faiha Specialized Diabetes Endocrine and Metabolism Center (FDEMC) Research (date of approval: 1/05/2021; protocol no: 66/31/21).

Author contributions

Haider Ayad Alidrisi: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Project administration, Writing — original draft preparation. Sameh Abed Odhaib: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Project administration, Writing — original draft preparation.Hussein Ali Nwayyir: Project administration, Writing — original draft preparation, Writing — review and editing, SupervisionAmmar Mohammed Saeed Almomin: Project administration, Writing — original draft preparation, Writing — review & editing, Supervision

Funding

Medical writing and editorial assistance were provided by KAPPA Training Consultancy and Research Ltd. and funded by a grant from Novo Nordisk Scientific Bureau for Medicines' Promotions. The authors take full responsibility for the content and conclusions stated in this manuscript. Novo Nordisk neither influenced the content of this publication nor was it involved in the study design, data collection, analysis or interpretation

Conflict of interests

The authors declare no conflict of interests.

REFERENCES

1. Lazzaroni E, Ben Nasr M, Loretelli C, et al. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. Pharmacol Res. 2021; 171: 105782, doi: 10.1016/j.phrs.2021.105782, indexed in Pubmed: 34302978.
2. Evert AB, Franz MJ. Why Weight Loss Maintenance Is Difficult. Diabetes Spectr. 2017; 30(3): 153–156, doi: 10.2337/ds017-0025, indexed in Pubmed: 28848306.
3. Bailey CJ, Flatt PR, Conlon JM. An update on peptide-based therapies for type 2 diabetes and obesity. Peptides. 2023; 161: 170939, doi: 10.1016/j.peptides.2023.170939, indexed in Pubmed: 36608818.
4. Iglay K, Hannachi H, Joseph Howie P, et al. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. Curr Med Res Opin. 2016; 32(7): 1243–1252, doi: 10.1185/03007995.2016.1168291, indexed in Pubmed: 26986190.

5. Davies MJ, D'Alessio DA, Fradkin J, et al. 30291106. Diabetes Care. 2018; 41(12): 2669–2701, doi: 10.2337/dci18-0033, indexed in Pubmed: 30291106.
6. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: . Diabetes Care. 2021; 44(Suppl 1): S111–S124, doi: 10.2337/dc21-S009, indexed in Pubmed: 33298420.
7. Davies MJ, Bergenstal R, Bode B, et al. NN8022-1922 Study Group. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA. 2015; 314(7): 687–699, doi: 10.1001/jama.2015.9676, indexed in Pubmed: 26284720.
8. Howell R, Wright AM, Clements JN. Clinical potential of liraglutide in cardiovascular risk reduction in patients with type 2 diabetes: evidence to date. Diabetes Metab Syndr Obes. 2019; 12: 505–512, doi: 10.2147/DMSO.S174568, indexed in Pubmed: 31118715.
9. Silva-Nunes J, Nascimento E, Louro J, et al. Liraglutide Effectiveness in Type 2 Diabetes: Insights from a Real-World Cohort of Portuguese Patients. Metabolites. 2022; 12(11), doi: 10.3390/metabo12111121, indexed in Pubmed: 36422260.
10. Zhou F, Jiang Lu, Guo J, et al. Degree of obesity and gastrointestinal adverse reactions influence the weight loss effect of liraglutide in overweight or obese patients with type 2 diabetes. Ther Adv Chronic Dis. 2023; 14: 20406223231161516, doi: 10.1177/20406223231161516, indexed in Pubmed: 36950020.
11. Rahmah A, Al-Isawi J, Mahdi O. The efficacy of once-daily liraglutide as an add-on to oral antidiabetic agents on weight reduction and glycemic control in obese patients with inadequately controlled type 2 diabetes: a retrospective analysis in relation to liraglutide dose escalation within a 7-month treatment period. International Journal of Diabetes in Developing Countries. 2020; 41(2): 266–272, doi: 10.1007/s13410-020-00878-5.
12. Bashier AMK, Hussain AA, Abdelgadir EI, et al. Liraglutide effect in reducing HbA1c and weight in Arab population with type2 diabetes, a prospective observational trial. J Diabetes Metab Disord. 2015; 14: 48, doi: 10.1186/s40200-015-0178-6, indexed in Pubmed: 26064864.
13. Yousef CC, Thomas A, Matar MAl, et al. Liraglutide effects on glycemic control and weight in patients with type 2 diabetes Mellitus: A real-world, observational study and brief narrative review. Diabetes Res Clin Pract. 2021; 177: 108871, doi: 10.1016/j.diabres.2021.108871, indexed in Pubmed: 34052248.
14. Ostawal A, Mocevic E, Kragh N, et al. Clinical Effectiveness of Liraglutide in Type 2 Diabetes Treatment in the Real-World Setting: A Systematic Literature Review. Diabetes Ther. 2016; 7(3): 411–438, doi: 10.1007/s13300-016-0180-0, indexed in Pubmed: 27350545.
15. Sethi BK, Viswanathan V, Kumar A, et al. Liraglutide in clinical practice: insights from LEAD programme. J Assoc Physicians India. 2010; 58: 18–22.
16. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020; 46(2): 100–109, doi: 10.1016/j.diabet.2019.101117, indexed in Pubmed: 31539622.
17. Gu J, Meng X, Guo Y, et al. The efficacy and safety of liraglutide added to metformin in patients with diabetes: a meta-analysis of randomized controlled trials. Sci Rep. 2016; 6: 32714, doi: 10.1038/srep32714, indexed in Pubmed: 27600499.
18. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. Diabetes Obes Metab. 2007; 9(6): 799–812, doi: 10.1111/j.1463-1326.2006.00686.x, indexed in Pubmed: 17924864.
19. Zinman B, Gerich J, Buse JB, et al. LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009; 32(7): 1224–1230, doi: 10.2337/dc08-2124, indexed in Pubmed: 19289857.
20. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009; 52(10): 2046–2055, doi: 10.1007/s00125-009-1472-y, indexed in Pubmed: 19688338.
21. Nauck M, Frid A, Hermansen K, et al. LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009; 32(1): 84–90, doi: 10.2337/dc08-1355, indexed in Pubmed: 18931095.
22. Nauck MA, Quast DR, Wefers J, et al. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021; 46: 101102, doi: 10.1016/j.molmet.2020.101102, indexed in Pubmed: 33068776.
23. Gough SCL, Bode B, Woo V, et al. NN9068-3697 (DUAL-I) trial investigators. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2014; 2(11): 885–893, doi: 10.1016/S2213-8587(14)70174-3, indexed in Pubmed: 25190523.
24. Abusnana S, Al Awadi F, Aly H, et al. Switching to a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) is associated with improved glycaemic control in a real-world population with type 2 diabetes mellitus in the United Arab Emirates: Results from the multicentre, prospective INTENSIFY study. Diabetes Res Clin Pract. 2023; 196: 110183, doi: 10.1016/j.diabres.2022.110183, indexed in Pubmed: 36436550.
25. Garvey WT, Birkenfeld AL, Dicker D, et al. Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial. Diabetes Care. 2020; 43(5): 1085–1093, doi: 10.2337/dc19-1745, indexed in Pubmed: 32139381.
26. Martinka E, Dravecká I, Tkáč I. Switching from Multiple Insulin Injections to a Fixed Combination of Degludec and Liraglutide in Patients with Type 2 Diabetes Mellitus: Results from the Simplify Study After 6 Months. Diabetes Ther. 2023; 14(9): 1503–1515, doi: 10.1007/s13300-023-01435-z, indexed in Pubmed: 37402960.
27. Unger J, Allison DC, Kaltoft M, et al. LIRA-PRIME investigators. Maintenance of glycaemic control with liraglutide versus oral antidiabetic drugs as add-on therapies in patients with type 2 diabetes uncontrolled with metformin alone: A randomized clinical trial in primary care (LIRA-PRIME). Diabetes Obes Metab. 2022; 24(2): 204–211, doi: 10.1111/dom.14566, indexed in Pubmed: 34622567.
28. Ciresi A, Vigneri E, Radellini S, et al. Liraglutide Improves Cardiovascular Risk as an Add-on to Metformin and Not to Insulin Secretagogues in Type 2 Diabetic Patients: A Real-life 48-Month Retrospective Study. Diabetes Ther. 2018; 9(1): 363–371, doi: 10.1007/s13300-017-0338-4, indexed in Pubmed: 29139081.
29. Simioni N, Berra C, Boemi M, et al. ReaL (NN2211-4118) Study Group*. Predictors of treatment response to liraglutide in type 2 diabetes in a real-world setting. Acta Diabetol. 2018; 55(6): 557–568, doi: 10.1007/s00592-018-1124-0, indexed in Pubmed: 29527621.
30. Wu H, Lu Z, Chen R, et al. Factors associated with gastrointestinal side effects after liraglutide treatment for type 2 diabetes. Front Endocrinol (Lausanne). 2023; 14: 1098032, doi: 10.3389/fendo.2023.1098032, indexed in Pubmed: 36793278.