Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

# Liraglutide effects on glycemic control and weight in patients with type 2 diabetes Mellitus: A real-world, observational study and brief narrative review

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ARTICLE INFO

*Article history:*
Received 25 December 2020
Received in revised form
6 April 2021
Accepted 24 May 2021
Available online 28 May 2021

*Keywords:*
Clinical outcomes
GLP-1 receptor agonist
Liraglutide
Saudi Arabia
Narrative review
Ministry of National Guard-Health Affairs

ABSTRACT

*Background:* Glycemic control and weight gain are two essential considerations in the pharmacological management of type 2 diabetes mellitus. Pharmacological agents are effective in lowering blood glucose levels but may result in significant weight gain. Liraglutide effectively maintains glycemic control while reducing weight.

*Methods:* This is a real-world study and brief narrative review of the effects of liraglutide on glycemic control and weight in adult patients with type 2 diabetes mellitus. The study uses data extracted from the electronic health record of the Ministry of National Guard-Health Affairs.

*Results:* In this study of 348 subjects, there was a statistically significant reduction in hemoglobin A1c of 0.9% ($P < .0001$) and weight of 2.3 kg ($P < .0001$). The majority (77.3%) were on concomitant insulin. Subjects with a baseline hemoglobin A1c greater than 9% had a significantly greater reduction than those below 9% (−0.7%; $P < .0001$). Those with a weight more than 100 kg had a significantly greater reduction than those below 100 kg (-0.9 kg; $P = .0096$).

*Conclusion:* In this real-world, observational study, liraglutide was shown to be effective in improving glycemic control and reducing weight in adult patients with type 2 diabetes mellitus.



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https://doi.org/10.1016/j.diabres.2021.108871
0168-8227/

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a major public health problem due to its association with significant morbidity, premature mortality, and increases in healthcare expenditures [1–3]. Globally, more than 300 million people have T2DM with the number predicted to rise to more than 500 million by 2030 [4]. Although the incidence and prevalence of T2DM vary by geographic region with the highest percentage (more than 80%) in those living in low-to-middle-income countries, there has been an upward trend in every country since 1980 [1]. With rapid economic development, lifestyle changes, and urbanization, the Middle East and North Africa are forecasted to have the highest prevalence of diabetes in the coming years [5]. Saudi Arabia is in the top 10 countries with the highest diabetes rates among adults with the prevalence rising from 7% to 32% from 1989 to 2009 [4].

T2DM is a chronic metabolic disease associated with microvascular (nephropathy, neuropathy, and retinopathy) and macrovascular (cardiovascular and cerebrovascular) complications over the long-term [4]. Patients with T2DM also have a 15% higher risk of all-cause mortality [1]. A *meta*-analysis published in 2010 found that diabetes is associated with an increased risk of coronary heart disease (CHD) (hazard ratio [HR]: 2.00; 95% CI 1.83–2.190); ischemic stroke (HR: 2.27; 95% CI 1.83–2.19); and deaths secondary to vascular disease (HR 1.73; 95% CI 1.51–1.98) [6]. Therefore, the management of T2DM aims to prevent the development of disease complications and halt the progression by improving glycemic control, which is measured by the glycated hemoglobin (HbA1c). A reduction in microvascular complications has been shown with a HbA1c $\leq$ 7% [7]. While the HbA1c goal is individualized based on patient characteristics, a HbA1c $\leq$ 7% is the aim for most non-pregnant adults [7]. Achieving a target HbA1c requires lifestyle modifications, dietary interventions, physical activity, and medications [8].

Several medications with different mechanisms of action are approved for the treatment of diabetes. Furthermore, a number of guidelines are available to guide the management of T2DM, and most of these guidelines recommend starting with lifestyle changes with or without metformin. Many patients with T2DM will require multiple hypoglycemic medications to achieve the target blood glucose levels [1]. The avoidance of hypoglycemia and weight gain are paramount considerations in selecting appropriate individualized drug therapy [9]. Good glycemic control is difficult to achieve due to many factors, including age, lifestyle, and environment [1]. The need to balance the risk of hypoglycemia and weight gain against the benefits of lowering the HbA1c must be carefully considered [4].

Weight gain is associated with many of the hypoglycemic medications (e.g., sulfonylureas, glinides, insulins, and thiazolidinediones) [9]. As weight increases, insulin resistance increases, necessitating higher doses of medications to achieve glycemic control. Medications that are weight neutral or enhance weight loss may be needed for weight management. These drugs are metformin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose cotransporter-2 inhibitors, or pramlintide [9].

GLP-1RAs, a type of incretin therapy, work by increasing insulin secretion, reducing glucagon secretion and hepatic glucose output, delaying gastric emptying, and increasing satiety [3]. GLP-1RAs are an option as monotherapy or in combination with other antihyperglycemic agents to manage T2DM. As a class they have the advantages of weight loss and low rates of hypoglycemia. A number of studies have shown a reduction in HbA1c from 0.9 to 1.6% and reduction in weight ranging from 0.2 to 7.2 kg with GLP-1 RAs [10]. Worldwide there are six approved GLP-1RAs—exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide [11].

Liraglutide (Victoza®) is one of the six approved GLP-1RAs worldwide [11]. It is a once-daily GLP-1 analog with a structure 97% homologous to endogenous human GLP-1 [12]. In comparison to endogenous GLP-1, it has an extended half-life (13 hrs vs. 2 min) [12]. It was approved by the Europeans Medicine Agency (EMA) and the United States Food and Drug Administration (US FDA) in 2009 and 2010, respectively [13].

While RCTs are the gold standard for establishing safety and efficacy of medical interventions, the strict criteria may exclude the typical patient seen in routine care [14]. Real-world studies have developed as a way to gain insight into diverse patient populations and clinical settings [14]. This real-world study will evaluate the effectiveness of liraglutide for the treatment of T2DM in routine clinical practice. This study evaluated glycemic control, weight, and adverse effects. Furthermore, the results of a narrative review of studies published since 2016 on the real-world effects of liraglutide are included.

## 2. Methods

### 2.1. *Study design*

This was a non-experimental, retrospective, observational study that used the BESTCare electronic health record (EHR). Data were extracted from the pharmacy records at each site and collected by the authors using a data collection form that did not include any patient identifiable information. Data were collected between November 2019 and March 2020. Fig. 1 shows the CONSORT diagram.

### 2.2. *Setting and subjects*

This multi-center study was conducted at three hospitals under the Ministry of National Guard-Health Affairs (MNG-HA): King Abdulaziz Hospital (Al Ahsa), Imam Abdulrahman Bin Faisal Hospital (Dammam), and King Khaled National Guard Hospital (Jeddah). MNG-HA is a large integrated healthcare system established in 1983 to provide state of the art medical care to the National Guard's soldiers and their dependents in all regions across the Kingdom of Saudi Arabia. The study included adults aged 18 years and older with T2DM (based on the International Classification of Diseases [ICD] 10th edition code) who initiated liraglutide treatment between January 2017 and December 2018 and received treatment for a minimum of three months and up to a maximum

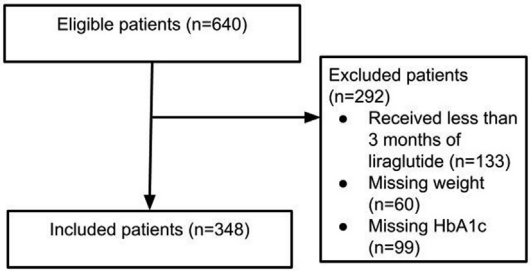


**Fig. 1 – CONSORT diagram.**

of 36 months. All patients were required to have an HbA1c and weight measured within 180 days of index date (baseline) and a follow-up at either 3–6 months, 7–12 months, or 13–24 months after initiation.

The study was approved by institutional review board of King Abdullah International Medical Research Center.

### 2.3. *Sample size*

The primary objectives were to assess the changes in HbA1c and weight in patients on liraglutide. By looking at a sample of the data collected early on from one center, there was a 0.5% (±1.5) reduction in HbA1c. At 90% power and 5% level of significance with an effect size of 0.33, the minimum required sample size for the study was estimated as 97 subjects. From the same sample, a 1.6 kg (±6.3) reduction in weight was seen. At 90% power and 5% level of significance, the minimum required sample size was estimated as 165 subjects. The larger sample size was chosen as the target sample size.

### 2.4. *Study outcomes*

The primary study outcomes were the change in HbA1c and weight from baseline. A secondary outcome was to evaluate the prevalence and type of adverse effects that were the reason for liraglutide discontinuation.

### 2.5. *Covariates*

The demographic characteristics collected were age and gender. The presence of the comorbidities hypertension, dyslipidemia, chronic kidney disease, and ischemic heart disease was taken from the BESTCARE EHR. Finally, the number and type of hypoglycemic agents was documented.

### 2.6. *Statistical analysis*

MS Excel was used to enter the data and SAS 9.4 software [15] for the analysis. The categorical data is presented as frequency and percentage and continuous data as mean and standard deviation. The change in HbA1c and weight variables were calculated by subtracting the baseline values from the follow-up measurements. The summary of the shift in weight and HbA1c variables identified the extreme outlier observations (below Q1 – 3*quartile range and Q3 + 3* quartile range) and excluded them from further model fitting. For weight change, the inclusion boundaries were from –23 kg to 19 kg, and for HbA1c change, the inclusion boundaries were from −7.2 to 5.4 kg. The proportion of adverse drug reactions and corresponding 95% confidence intervals were estimated using the Wilson method.

Linear mixed model analysis was used to measure the significance of the effect of liraglutide in reducing HbA1c and weight. There was a further analysis of the influence of the covariates on the change of HbA1c and weight, including the time in the model. The effect of time was assumed to be the effect of treatment since the treatment was given after the baseline measurement. All models considered time as the repeated component for each subject and conveniently selected compound symmetry as the variance–covariance structure. Maximum likelihood method was used for estimation. A $P$ value<0.05 was considered as evidence for a significant effect.

## 3. Results

### 3.1. *Demographic and clinical characteristics*

The baseline demographic and clinical characteristics are presented in Table 1. The mean duration of liraglutide use was 22.5 months (±8). The majority of patients were female (210, 60.3%) and below the age of 60 years (210, 60.3%). The mean age was 54.9 years (±11.3). The baseline mean HbA1c was 9.1% (±1.7) and mean weight was 101.1 kg (±1.7). The baseline HbA1c for males was 9.2% (±1.7) and females was 9.1% (±1.7). The baseline weight for males was 106.9 kg (±20.2) and females was 97.2 (±19.5). The majority were on concomitant insulin (269, 77.3%) and at least one oral hypoglycemic agent (183, 81.9%). Metformin was the most frequently used oral hypoglycemic agent in 279 (80.2%) of the subjects. Of those on concomitant insulin, most were on multiple daily injections. The majority (284, 81.6%) had a comorbidity with dyslipidemia being the most common (245, 70.4%) followed by hypertension (208, 59.8%).

### 3.2. *Change in HbA1c*

The overall effect for HbA1c is shown in Fig. 2 and was statistically significant (-0.9%, $P < .0001$). There were statistically significant differences in the HbA1c levels compared to baseline at 3–6 months 7–12 months, and 13–24 months ($P < .0001$). The changes in HbA1c with time are shown in Table 2. The HbA1c was 9.1% (±1.7) at baseline and 8.2% (±1.8) at 13–24 months. No statistically significant change was seen for HbA1c with any covariates as shown in Table 3. Fig. 3 shows the changes in HbA1c with covariates. The change in HbA1c between subjects with an HbA1c greater than 9% and<9% was statistically significant (0.67%, $P < .0001$).

### 3.3. *Change in weight*

There was an overall statistically significant effect for weight reduction of −2.3 kg shown in Fig. 4 ($P < .0001$). There were also statistically significant ($P < .0001$) changes in weight from baseline at 3–6 months, 7–12 months, and 13–24 months. The

**Table 1 – Baseline characteristicse.**

| Variable Name | Level | Frequency (%) |
|---|---|---|
| Hospital | | |
| | Dammam | 62 (17.8) |
| | Al Ahsa | 79 (22.7) |
| | Jeddah | 207 (59.5) |
| Gender | | |
| | Male | 138 (39.7) |
| | Female | 210 (60.3) |
| Age | | |
| | <60 Years | 210 (60.3) |
| | >60 Years | 138 (39.7) |
| Comorbidity | | |
| | Hypertension | 208 (59.8) |
| | Dyslipidemia | 245 (70.4) |
| | Chronic kidney disease | 25 (7.2) |
| | Ischemic heart disease | 34 (3.4) |
| Oral diabetes medication | | 288 (82.8) |
| Number of oral diabetes medications | | |
| | One | 183 (52.6) |
| | Two | 93 (26.7) |
| | Three | 12 (3.4) |
| Type of oral diabetes medication | | |
| | Metformin | 279 (80.2) |
| | Sulfonylureas | 68 (19.5) |
| | Sitagliptin | 51 (14.7) |
| | Pioglitazone | 11 (3.2) |
| Insulin use | | 269 (77.3) |
| Multiple daily insulin injections | | 205 (58.9) |

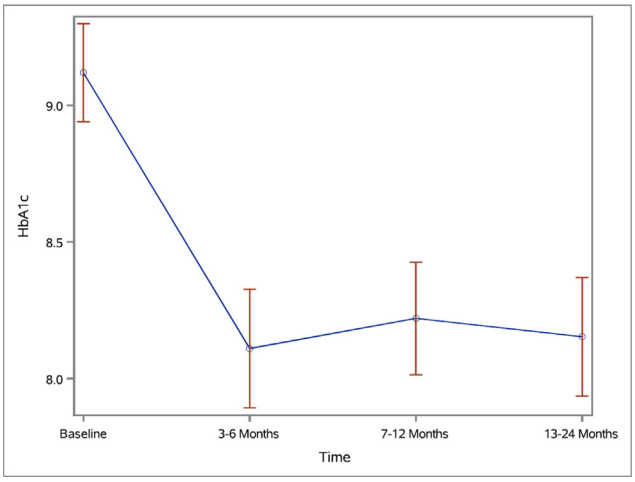


**Fig. 2 – Overall effect on HbA1c.**

**Table 2 – Effect of Liraglutide on HbA1c and Weight.**

| | HbA1c Mean (SD) | Weight Mean (SD) |
|---|---|---|
| **Baseline** | 9.12 (1.7) | 101.08 (20.3) |
| **3–6 Months** | 8.11 (1.7) | 98.94 (19.9) |
| **7–12 Months** | 8.22 (1.7) | 98.82 (20.8) |
| **13–24 Months** | 8.15 (1.8) | 98.44 (20.6) |
| **P- value** | <0.0001 | <0.0001 |

changes in weight with time are shown in Table 2. No statistically significant change was seen for weight with any covariates as shown in Table 3. Fig. 5 shows the changes in weight with covariates. The change in weight between subjects with a weight greater than 100 kg and<100 kg was statistically significant (0.87 kg, $P = .0096$).

### 3.4. *Adverse events*

There were 58 (16.7%) subjects who discontinued liraglutide. Nine cases were due to an adverse event: gastrointestinal (7), endocrine/metabolic (1), central nervous system (1). The remainder discontinued due to an unspecified cause. There was no association between gender and discontinuation due to an adverse drug event (males: 18.1%, females: 15.7%, $P = .557$).

### 3.5. *Narrative review*

This brief narrative review was conducted to collect evidence on the clinical effectiveness and adverse effects of liraglutide in real world studies using PubMed and Google Scholar. In Google Scholar, the filter for "since 2016" was used to capture literature published after the systematic literature review by Ostawal et al in 2016 [13]. Various combinations of the following search terms were used: "clinical effectiveness", liraglutide, "real world", "glycemic control", "hemoglobin A1c", and weight. Eleven studies with a minimum follow up of 12 months are included in the review. Four investigators extracted data on clinical effectiveness and adverse drug

**Table 3 – Effect of covariates in the change of HbA1c and Weight.**

| Parameter | Level | HbA1c | | Weight | |
|---|---|---|---|---|---|
| | | Estimate (SE) | P-value | Estimate (SE) | P- value |
| Gender | | | | | |
| | Female | 0.05 (0.11) | 0.651 | −0.42 (0.34) | 0.228 |
| | Male | – | – | – | – |
| Time | 13–24 Months | −1.02 (0.09) | <0.0001 | −2.75 (0.29) | <0.0001 |
| | 7–12 Months | −0.92 (0.087) | <0.0001 | −2.28 (0.28) | <0.0001 |
| | 3–6 Months | −0.82 (0.09) | <0.0001 | −1.77 (0.28) | <0.0001 |
| | Baseline | – | – | – | – |
| Age | | | | | |
| | 60 or above | 0.09 (0.11) | 0.388 | 0.35 (0.34) | |
| | Below 60 | – | – | | |
| Time | 13–24 Months | −1.02 (0.09) | <0.0001 | −2.75 (0.29) | <0.0001 |
| | 7–12 Months | −0.92 (0.09) | <0.0001 | −2.28 (0.28) | <0.0001 |
| | 3–6 Months | −0.82 (0.09) | <0.0001 | −1.78 (0.28) | <0.0001 |
| | Baseline | – | – | – | – |
| Insulin use | | | | | |
| | No | −0.05 (0.13) | 0.701 | −0.72 (0.41) | 0.079 |
| | Yes | – | – | – | |
| Time | 13–24 Months | −1.02 (0.09) | <0.0001 | −2.76 (0.29) | <0.0001 |
| | 7–12 Months | −0.92 (0.09) | <0.0001 | −2.29 (0.28) | <0.0001 |
| | 3–6 Months | −0.8173 (0.09) | <0.0001 | −1.78 (0.28) | <0.0001 |
| | Baseline | – | – | – | – |
| Multiple daily injections of insulin | | | | | |
| | No | −0.11 (0.14) | 0.435 | −0.12(0.27) | 0.259 |
| | Yes | – | – | – | – |
| Time | 13–24 Months | −0.98 (0.1) | <0.0001 | −2.56 (0.30) | <0.0001 |
| | 7–12 Months | −0.88 (0.1) | <0.0001 | −2.02 (0.29) | <0.0001 |
| | 3–6 Months | −0.85 (0.1) | <0.0001 | −1.55 (0.30) | <0.0001 |
| | Baseline | – | – | – | – |
| Oral diabetes medications | | | | | |
| | No | 0.16 (0.14) | 0.263 | 0.45 (0.45) | 0.323 |
| | Yes | – | – | – | – |
| Time | 13–24 Months | −1.02 (0.09) | <0.0001 | −2.74(0.29) | <0.0001 |
| | 7–12 Months | −0.92 (0.09) | <0.0001 | −2.28 (0.28) | <0.0001 |
| | 3–6 Months | −0.82 (0.09) | <0.0001 | −1.78 (0.28) | <0.0001 |
| | Baseline | – | – | – | – |

reactions from the studies using a template. Quality assessment and risk of bias were not assessed. Results are shown in Table 4.

Ostawal et al found 106 publications of liraglutide in type 2 diabetes in real-world settings and reported changes in HbA1c from baseline to study end and found the mean HbA1c change from baseline was −0.6% to −2.26% [13]. For effects on body weight, the authors identified 74 publications with the mean change in weight from −1.3 to −8.65 kg [13]. For safety and tolerability, 52 publications reported data on adverse effects showing rates ranging from 0% to 64.3%. Gastrointestinal effects were most commonly reported with rates of 0.51% to 42.9%. Mean changes in HbA1c differed by geographic location: Europe (−0.8% to −1.9%); United States (−0.8% to −0.99%); and Asia-Pacific (−0.6% to −2.26%). Mean change in weight also varied by geographic location: Europe (−2.4 kg to −6.5 kg); United States (−2.9 kg to −1.3 kg); and Asia-Pacific (−1.3 kg to −8.7 kg). There was significant weight loss in patients who used liraglutide as monotherapy and along with oral hypoglycemic medications.

In this narrative review all studies involved a secondary analysis of data previously collected from the patient medical record or a database. The geographical scope of this review includes studies from Europe (n = 7) and Asia-Pacific (n = 4). Most of the studies assessed liraglutide without an active comparator. One study [16] evaluated pooled outcomes associated with GLP-1 RA therapy (liraglutide, exenatide, and once-weekly exenatide). Another study [17] compared the effectiveness of liraglutide, dulaglutide, and exenatide. Most studies [16–22] showed statistically significant differences in glycemic control after liraglutide treatment. Weight loss was statistically significant after treatment with liraglutide in seven studies [17–19,21–24].

## 4. Discussion

The aim of this multicenter, retrospective, observational study was to evaluate the clinical effectiveness (i.e., glycemic control and weight change) of liraglutide in a real-world setting. While many studies around the world have evaluated

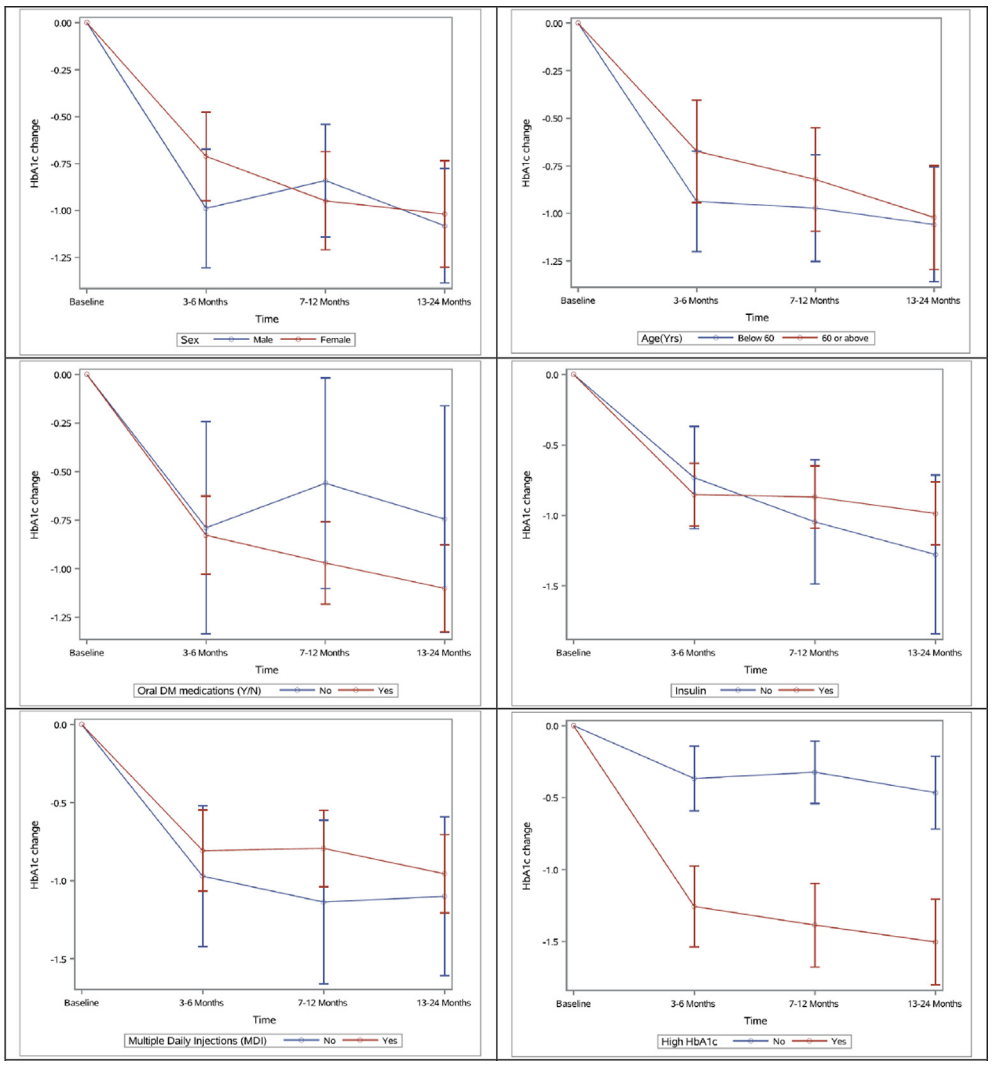


**Fig. 3 – Change of HbA1c with covariates.**

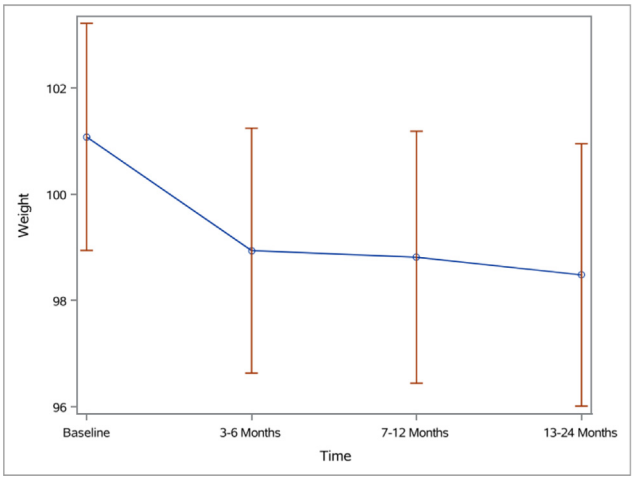


**Fig. 4 – Overall effect on weight.**

the real-world effects of liraglutide, few have been conducted in the Kingdom of Saudi Arabia. The results of this study can be compared to Albarkah et al who found a statistically significant HbA1c reduction of 0.84% with liraglutide 1.2 mg; however, there were no statistically significant effects on weight [20]. Consistent with RCTs, the findings from this study showed treatment with liraglutide was characterized by statistically significant improvements in glycemic control (-0.9%, $P < .0001$) and weight (-2.3 kg, $P < .0001$). The subjects had a higher baseline mean HbA1c (9.12% ± 1.7), weight (101.08 kg ± 20.3), and the majority (58.9%) were on multiple daily injections of insulin. Subjects with an elevated baseline HbA1c (above 9%) and weight (above 100 kg) had greater improvements.

Although the results for glycemic control and weight are well-aligned with RCTs, the magnitude of the effect for HbA1c is less than observed while the weight effects are similar. In the LEAD trials, HbA1c reductions as high as 1.6% were observed [27]. In the systematic review and *meta*-analysis of RCTs conducted by Potts et al to evaluate the effect of GLP-1RAs on weight loss in T2DM, they found an average weight loss of −1.01 kg to −1.51 kg with liraglutide [28]. Clinical effectiveness has widely varied by region as identified previously by Ostawal et al [13] and in this narrative review. Different patterns of response have been

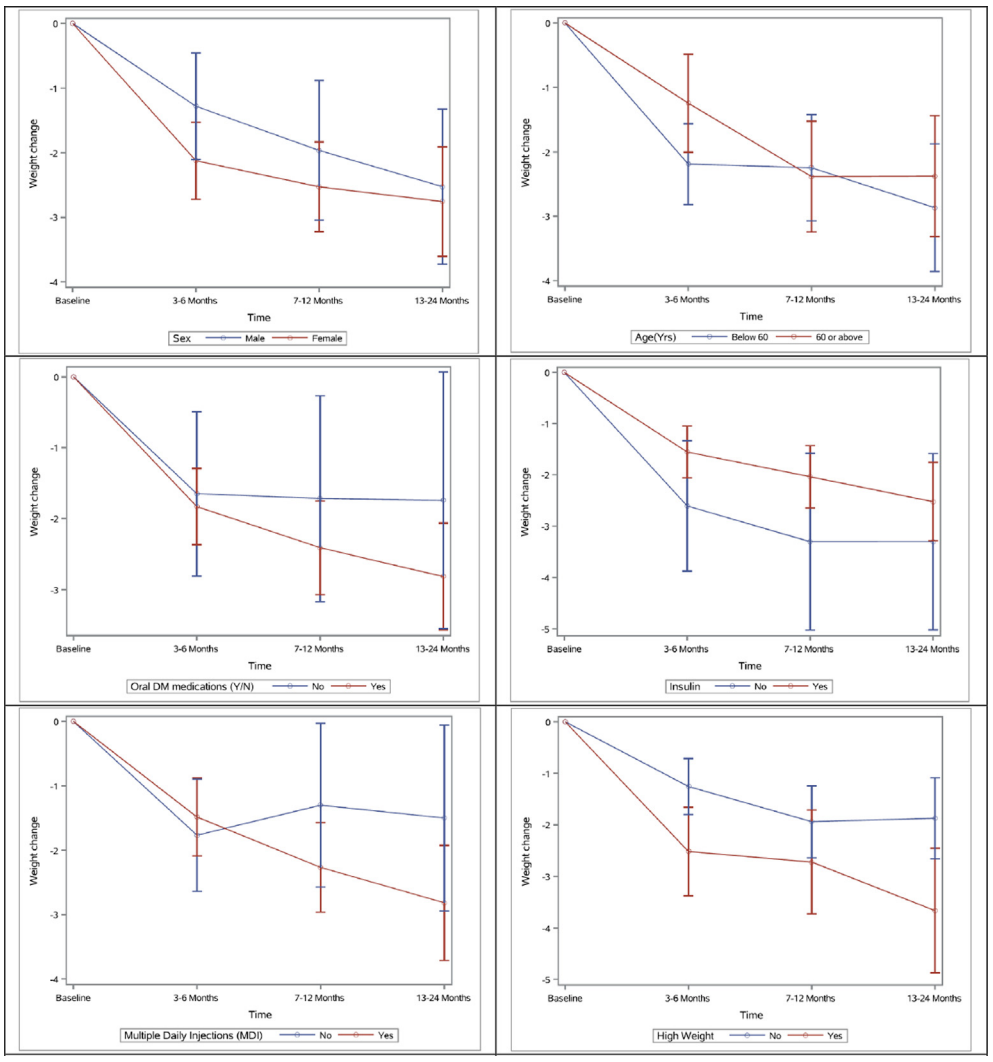


**Fig. 5 – Change of weight with covariates.**

attributed to factors such as age, liraglutide dose, baseline HbA1c, duration of T2DM, and concomitant treatments. A higher baseline HbA1c, longer duration of T2DM, and longer duration of insulin treatment have been shown to counter the effects of liraglutide [25,29]. Gomez-Peralta et al found a positive correlation between weight reduction and a higher baseline weight, longer duration of treatment with liraglutide, and the interaction between time and concomitant metformin [25]. Another real-world study found lower HbA1c reductions in patients who initiated insulin either before or around the same time as starting a GLP-1RA [30]. In the study conducted by Simioni et al, predictors of achieving an HbA1c reduction of $\geq$ 1% were the following baseline characteristics: mean duration of T2DM of 10.2 years, metformin ± sulfonylurea treatment, mean HbA1c of 10.2%, mean fasting plasma glucose of 223.0 mg/dL, and liraglutide used as add-on treatment [22]. Lapolla et al found that age, baseline HbA1c, and prior metformin monotherapy were significant positive predictors of HbA1c reduction after 12 months [31]. For effects on weight, they found a positive correlation between baseline weight and weight loss at 12 months and negative correlation with prior insulin treatment [31].

This study is important because it reports outcomes over an extended period and at multiple time points. Morieri et al evaluated the effects of dulaglutide, once weekly exenatide, and liraglutide between 2010 and 2018 but only included HbA1c and weight from the first follow-up visit 3–12 months after baseline. The mean duration of treatment in this study was 22.5 months (±8). Discontinuation was relatively high (58 subjects, 16.7%) with nine cases attributable to an adverse drug reaction—seven were gastrointestinal effects [32]. Since no reason for discontinuation was available for 49 patients, no firm conclusions can be drawn about prevalence of adverse effects. Some patients may have discontinued for reasons unrelated to adverse effects such as prior to or after having bariatric surgery or a change in patient preference.

## 5. Limitations

There are a few limitations to be highlighted. Foremost, the results are subject to bias and confounding [14]. There may

**Table 4 – Real-world studies on effectiveness of liraglutide.**

| Author, Country, Year | Study aims | Sample | Baseline glycemic control | Baseline weight | Glycemic control outcome | Weight outcome | Adverse events |
|---|---|---|---|---|---|---|---|
| Kaur et al, India, 2016 [18] | To evaluate the effect of liraglutide on glycemic control and weight in obese patients with T2DM followed for 1 year | N = 96;male 61%; age 50.9 years (±9.6); duration of DM 11.6 years (±6.3); | 8.9% (±1.3) | 98.9 kg (±16.0) | 7.4% (±1.2)<br>P < .01 | 93.8 kg (±15.0)<br>P < .05 | Total number: 32<br>Diarrhea (n = 11), nausea (n = 14) |
| Chaudhuri et al, India, 2016 [19] | To evaluate the effect of liraglutide on weight, blood pressure, glycemic control, and safety and tolerability for up to 40 months | N = 39; male: female ratio1.6 to1; age 47.9 years (±11); duration of DM 6.56 years (±4.55) | 9.08% (±1.54) | 88.3 kg (±10.68) | 7.3% (±1.02)<br>P < .0001 | 80.8 kg (±11.83)<br>P < .0001 | Total number: 13<br>Gastrointestinal (n = 8) |
| Albarkah et al,[17] Saudi Arabia, 2019 [20] | To measure changes in HbA1c, weight, and risk of hypoglycemia with liraglutide in patients followed for 12 months | N = 38; mean age 50.6 years (±10.8); male 44.7%; duration of DM 13.5 years (±7.4) | 0.6 mg dose: 9.3% (±1.9)<br>1.2 mg dose: 8.7% (±1.4)<br>1.8 mg dose: 8.5% (±1.0) | 0.6 mg dose: 91.2 kg (±15.0)<br>1.2 mg dose: 107.2 kg (±24.5)<br>1.8 mg: 110.4 kg (±15.8) | 0.6 mg dose: 8.8% (±1.6) NS<br>1.2 mg dose: 7.9% (±1.4) P = .003<br>1.8 mg dose: 8.6% (±1.2) NS | 0.6 mg dose: 88.2 kg (±15.3) NS<br>1.2 mg dose: 103.0 kg (±21.6) NS<br>1.8 mg: 110.9 kg (±16.5) NS | 1 mild case of hypoglycemia |
| Gomex-Peralta et al, Spain, 2018 [25] | To study the response of clinical variables (e.g., HbA1c, body weight) over 24 months of liraglutide treatment in real-world clinical setting | N = 799;<br>mean age 55.9 years (±12);<br>male 50%; duration of DM 8.8 years (±7.3) | 8.4% (±1.7) | 104.4 kg (±19.5) | After 6 months of treatment: 1.4%<br>After 12 months of treatment: 1.5%<br>60% of participants reached a target HbA1c of < 7% after 6 months of treatment | Weight loss ranged from 5 kg to 10 kg throughout the course of treatment | Not reported |
| Morieri et al, Italy, 2020 [17] | To compare the effectiveness of dulaglutide, liraglutide, and once weekly exenatide in real world clinical practice and conduct a *meta*-analysis of observational studies comparing the same GLP-1RAs | • N = 2148 (liraglutide, 1371; dulaglutide, 849; exenatide, 198)LiraglutideMale 61.3%Mean age: 59.9 years (±9.8)Duration of DM: 9.6 years (±6.6) DulaglutideMale 65.6% Mean age: 62.4 years (±9.7)Duration of DM: 9.9 years (±6.8)ExenatideMale 60.1%Mean age: 60.1 years (±8.6)Duration of DM: 8.6 years (±5.4) | **Liraglutide**<br>8.3% (±1.3)<br>**Dulaglutide**<br>8.2% (±1.2)<br>**Exenatide**<br>8.2% (±1.1) | **Liraglutide**<br>100.0 kg (±18.6)<br>**Dulaglutide**<br>95.5 kg (±18.1)<br>**Exenatide**<br>102.1 kg (±19.2) | **Liraglutide**<br>7.6% (±1.3)<br>Change: −0.7% (±1.4)<br>P < .05<br>**Dulaglutide**<br>7.2% (±1.2)<br>Change: −1.0 (±1.4)<br>P < .05<br>**Exenatide**<br>7.4% (±1.2)<br>Change: −0.8 (±1.4)<br>P < .05 | **Liraglutide**<br>97.2 kg (±18.5)<br>Change: −2.6 kg (±4.2)<br>P < .05<br>**Dulaglutide**<br>92.8 kg (±18.3)<br>Change: −2.8 kg (±4.7)<br>P < .05<br>**Exenatide**<br>99.5 kg (±19.7)<br>Change: −2.7 kg (±4.4)<br>P < .05 | Not reported |
| Melzer-Cohen et al Israel, 2019, [21] | To compare glycemic control and other clinically important outcomes at 24 months between patients with T2DM who continued treatment with liraglutide for 12 months and those who discontinued treatment earlier in a real life setting | • N = 2695Continuers Mean age 60.1 years (±9.1) Male 52.8%≥ 10 years in diabetes registry: 59.1% Discontinuers60.3 years (±9.9)Male 54.9%≥ 10 years in diabetes registry: 60.5% | Prematching *Continuers*: 8.9% (±1.3)<br>*Discontinuers*: 8.9% (±1.4)<br>P = .238<br>Postmatching<br>*Continuers*: 9.0% (±1.3)<br>*Discontinuers*: 9.0% (±1.4)<br>P = .814 | Not reported | Prematching *Continuers*: −0.78% (±1.5)<br>*Discontinuers*: −0.31% (±1.5)<br>P < .001<br>Postmatching<br>*Continuers*: −0.80% (±1.5)<br>*Discontinuers*: −0.32% (±1.5)<br>P < .001 | Prematching *Continuers*: −3.5 kg (±6.6)<br>*Discontinuers*: −1.3 kg (±7.4)<br>P < .001<br>Postmatching<br>*Continuers*: −3.6 kg (±6.5)<br>*Discontinuers*: −1.3 kg (±7.4)<br>P < .001 | Not reported |

**Table 4 – (continue)**

| Author, Country, Year | Study aims | Sample | Baseline glycemic control | Baseline weight | Glycemic control outcome | Weight outcome | Adverse events |
|---|---|---|---|---|---|---|---|
| Qiao et al, Germany, 2017 [16] | To investigate real world treatment outcomes and tolerability of GLP-1 receptor agonist therapy in primary care practices in Germany using the Disease Analyzer database with patients who had up to 18 months of follow-up | N = 544 (347 liraglutide, 89 exenatide, 108 exenatide once weekly);<br>mean age 57.9 years (±10.6);<br>male 54% | 8.3% (±1.4) | 106.3 kg (±20.3) | After 6 months of GLP-1RA treatment:<br>7.4 (±1.2)<br>*P* < .001<br><br>After 7–12 months of GLP-1RA treatment:<br>7.6 (±1.3)<br>*P* < .001<br><br>After 13–18 months of GLP-1RA treatment:<br>7.6 (±1.4)<br>*P* < .001 | After 6 months of GLP-1RA treatment:<br>103.9 kg (±21.2)<br>NS<br><br>After 7–12 months of GLP-1RA treatment:<br>105.2 kg (±22.1)<br>NS<br><br>After 13–18 months of GLP-1RA treatment:<br>104.3 kg (±21.9)<br>NS | No significant changes in occurrence of gastrointestinal adverse events or hypoglycemia but numbers not reported |
| Simioni et al, Italy, 2018 [22] | To identify subgroups or classes of patients with T2DM who were more likely to have an improved response to liraglutide due to specific clinical and socio-demographic characteristics | N = 1723;<br>mean age 58.9 years (±9.5);<br>male 54.9%; duration of DM 9.6 years (±<br>7.1) | 8.3% (±1.4) | Not reported for overall population | Class 1: HbA1c greater than 9.1%: −2.2 (±1.5)<br><br>Class 2: 8.2% < HbA1c ≥ 9.1%: −1.0 (±1.1)<br><br>Class 3: 7.5% < HbA1c ≥ 8.2% and diabetes duration ≤ 5 years: −0.9 (±1.0)<br><br>Class 4: 7.5% < HbA1c ≥ 8.2% and diabetes duration greater than 5 years: −0.5 (±0.9)<br><br>Class 5: HbA1c ≤ 7.5%: −0.1 (±0.8)<br><br>*P* < .0001 | Class 1: HbA1c greater than 9.1%: −2.5 kg (±6.1)<br><br>Class 2: 8.2% < HbA1c ≥ 9.1%: −4.3 kg (±5.3)<br><br>Class 3: 7.5% < HbA1c ≥ 8.2% and diabetes duration ≤ 5 years: −3.7 kg (±5.2)<br><br>Class 4: 7.5% < HbA1c ≥ 8.2% and diabetes duration greater than 5 years: −3.1 kg (±4.7)<br><br>Class 5: HbA1c ≤ 7.5%: −3.7 kg (±5.8)<br><br>*P* = .03 | Not reported |
| Martinez et al, France, 2017 [24] | To investigate the effectiveness of liraglutide in people with T2DM treated within the primary care physician (PCP) and specialist care center | • − N = 3152(1398 PCPand 1754 specialist care) PCPMean age 60.1 years (±10.5)Male 55.7%Median duration of DM: 8 years (5–12)SpecialistMean age 57.6 years (±10.4)Male 50.9%Median duration of DM: 10 years (5–15) | PCP :<br>8.53% (±1.48)<br><br>Specialist:<br>8.56% (±1.5) | PCP:<br>92.6 kg (±19.3)<br><br>Specialist:<br>98.1 kg (±20.2) | PCP:<br>−1.22% (-1.31; −1.12)<br>*P* < .0001<br><br>Specialist:<br>−0.80% (-0.9; − 0.71)<br>*P* < .0001 | PCP:<br>−4.4 kg (-4.8; −3.9]<br>*P* < .0001<br><br>Specialist:<br>−3.8 kg (-4.2; − 3.4)<br>*P* < .0001 | Hypoglycemia<br>-PCP 1%<br>-Specialist 7.9%<br><br>Gastrointestinal<br>-PCP 4.5%<br>-Specialist 16.1%<br><br>Cardiovascular<br>-PCP 0.9%<br>-Specialist 1.6% |

**Table 4 – (continue)**

| Author, Country, Year | Study aims | Sample | Baseline glycemic control | Baseline weight | Glycemic control outcome | Weight outcome | Adverse events |
|---|---|---|---|---|---|---|---|
| Berkovic et al, Croatia, 2017 [26] | To assess the glycemic efficacy and extra-glycemic effects of liraglutide during 36 months' follow up of individual's with poorly regulated T2DM under routine clinical practice | N = 207;<br>mean age 53.3 years (±9.4);<br>male 45.9%;<br>duration of diabetes 8.3 years (±4.9) | 8.5% (±1.3) | Not reported | After 6 months of treatment:<br>7.3% (±0.97)<br>*P* < .05<br><br>After 12 months of treatment:<br>7.3% (±1.1)<br>*P* < .05<br>After 18 months of treatment:<br>7.3% (±1.1)<br>*P* < .05<br><br>After 24 months of treatment:<br>7.4% (±1.3)<br>*P* < .05<br><br>After 36 months of treatment:<br>7.1% (±0.9)<br>*P* < .05 | Not reported | Not reported |
| Overbeek et al, Netherlands, 2018 [23] | To compare the outcomes over 12 months in obese people with T2DM who previously received oral antidiabetic therapy and either initiated treatment with liraglutide or basal insulin supported oral therapy (BOT) using the PHARMO Database Network | • – N = 1157 (544 liraglutide and 613 BOT)Liraglutide Unmatched Mean age, 57.5 years (±9.9) Male 52% Matched Mean age, 58.3 years (±10.3) Male 44% BOT Unmatched Mean age, 62.5 years (±11.1) Male 35% Matched Mean age, 61.3 years (±10.5) Male 45% | Liraglutide<br>Unmatched<br>68.4 mmol/mol (±13.3)<br><br>Matched<br>68.1 mmol/mol (±13.8)<br><br>BOT<br>Unmatched<br>70.1 mmol/mol (±13.2)<br>Matched<br>70.2 mmol/mol (±12.8) | Liraglutide<br>Unmatched<br>115.9 kg (±17.8)<br><br>Matched<br>115.4 kg (±17.3)<br><br>BOT<br>Unmatched<br>106.1 kg (±16.5)<br>Matched<br>107.7 kg (±17.3) | Least square mean change at 12 months<br><br>Liraglutide<br>-12.2 mmol/mol (-14.1; −10.4)<br><br>BOT<br>-8.8 mmol/mol (-10.6; −7.0)<br><br>Liraglutide vs BOT:<br>−3.4 mmol/mol (-5.8;-1.0)<br>*P* = .0053 | Least square mean change at 12 months<br><br>Liraglutide −6.0 kg (-7.7;-4.4)<br><br>BOT −1.6 kg (-3.1; −0.1)<br><br>Liraglutide vs BOT: −4.4 kg (-6.4; −2.5)<br>*P* < .0001 | Not reported |

have been inconsistencies in data collection with missing data elements possibly affecting statistical validity. Using prescription orders to capture medication use may have introduced misclassification bias. While prescription orders indicate a drug is prescribed, it does not mean the patient took the medication. There was no assessment of adherence. Not all confounding variables were available. Duration of diabetes was not readily available in the BESTCare EHR. Additionally, there were changes in diabetes therapy such as addition of medications or changes in insulin doses that could have contributed to the changes in HbA1c during the study period. This study does not account for the amount of time on any specific therapy other than liraglutide. Finally, even though the Ministry of National Guard-Health Affairs is a large, integrated health care system, subjects may not be representative of the population.

## 6. Conclusion

Liraglutide used either alone or in combination with other hypoglycemic agents was effective at reducing HbA1c and weight in patients with T2DM in this real-world setting. The findings confirm those seen in RCTs. This study is helpful in evaluating the effects of liraglutide in this region of the world. The brief narrative review places the results within context and demonstrates the variable effects of medication in different populations.

## Funding

The authors received no funding from an external source.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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