Original Article

Effectiveness, tolerability, and pattern of liraglutide treatment use for weight loss: a mixed-methods cohort study

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ABSTRACT

The prevalence of obesity is increasing worldwide including in Saudi Arabia. This study assessed the effectiveness and tolerability of 3 mg liraglutide for weight management of patients attending the Obesity Clinic at a secondary care university hospital in Riyadh, Saudi Arabia. This is an observational, single-center cohort study including a retrospective chart review to assess the effectiveness, and a to investigate the pattern of use and tolerability. All adult patients initiated on 3 mg liraglutide for weight loss were included (July - December 2019). The primary outcomes were mean weight change and mean BMI change after four months of using the medication. Secondary outcomes included tolerability and pattern of use. The study enrolled 105 patients, using a per-protocol analysis to assess effectiveness, only 36 (34.3%) had complete data until the fourth month from baseline. The mean difference in weight was 5.92± 5.55(p-value < 0.001). The percent change in body weight was -5.76% (range 2.17% - 22.69%). Half of the patients (n=18) lost ≥ 5% of their body weight. There was a significant reduction in BMI from baseline (2.24 kg/m2; range 1.56 – 2.91, p-value < 0.001). Of the 65 patients who responded to the cross-sectional survey, 55.4% continued using liraglutide for 4 months. The reason for stopping liraglutide was mostly side effects (38.5%). The use of diet and/or exercise remained constant across the 4 months at 50%. In this retrospective evaluation, 3.0 mg of once-daily liraglutide resulted in a clinically significant reduction in body weight, with no serious side effects.

Keywords: Liraglutide, GLP-1 analog, Weight reduction, Obesity, Pharmacological therapy

Introduction

Obesity is classified as a BMI of ≥30 kg/m² and is defined as an excessive fat accumulation imposing a health risk [1]. It is a known risk factor for several common chronic conditions including diabetes mellitus, cardiovascular disease, osteoarthritis, obstructive sleep apnea, cancer, and back pain [2, 3]. Obesity has now also been established as an important risk factor for COVID-19 and SARS-CoV-2 breakthrough infection [4, 5]. The choices for the treatment of obesity include lifestyle changes, pharmacotherapy, and bariatric surgery [6-8]. Obesity is highly prevalent in the world, with more than 1.9 billion overweight adults, and over 650 million obese in 2016 [9]. In Saudi Arabia, studies reported the prevalence of obesity, with a higher rate in women compared to men [10, 11]. Achieving a weight reduction of 5%-10% by diet (500 Kcal/day) and exercise alone is challenging. If lifestyle intervention fails, the addition of pharmacological treatment is recommended [6, 12]. Pharmacological treatment of increased fat mass should be initiated particularly when cardiometabolic risk factors are present. A category of obese individuals may not be at high risk for cardiovascular complications; these individuals are described as having metabolically healthy obesity. Whereas, metabolically

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unhealthy individuals are at increased risk of cardiovascular disease, even though they have normal BMI [13, 14]. Among the medications increasingly used for weight management is liraglutide.

Liraglutide is a glucagon-like peptide-1receptor agonist (GLP-1), which was initially approved by the FDA as an adjunct to dietary therapy and exercise for type 2 diabetes management. It was later commissioned, in 2014, by the FDA for the treatment of obesity [15]. It exerts its effect by multiple mechanisms including working in the pancreas to enhance glucose-stimulated insulin secretion, reducing inappropriately elevated levels of glucagon, delaying gastric emptying, and enhancing satiety by central effects on the hypothalamus [15].

Efficacy, safety, and tolerability of liraglutide, as a treatment for weight management, have been studied in randomized clinical trials involving populations from different countries. Findings showed that the use of liraglutide, accompanied by diet and exercise, was associated with significant weight loss. Mild to moderate drug-related side effects, such as nausea and vomiting was reported [16-18].

Few studies have been published on weight management with liraglutide in real-life settings. Findings from retrospective studies revealed that treatment with liraglutide resulted in clinically significant weight reduction, and comparable side effects to that reported in randomized clinical trials [7, 19, 20]. A single prospective study investigating the effectiveness of liraglutide on weight loss, in real-life practice, was also retrieved. Similarly, liraglutide combined with diet and exercise was found to be an effective agent in weight reduction [21]. In Saudi Arabia, one retrospective study was carried out to evaluate the effect of liraglutide on weight and glycemic control among adult patients with type 2 diabetes. A significant difference in weight loss was reported in that study [22]. However, to our knowledge, no study assessed the pattern of use of liraglutide among obese patients in real-world settings. This study was conducted, to assess the effectiveness, tolerability, and pattern of use of liraglutide as a treatment for obesity/overweight in a cohort of the Saudi population.

Materials and Methods

Study design and setting

This was an observational, single-center study with two stages. Stage 1 was a retrospective chart review and stage 2 was a cross-sectional survey to investigate the pattern of use and prevalence of side effects. The study was conducted at a secondary care hospital that offers an obesity clinic in Riyadh Saudi Arabia. Patients who started Liraglutide for weight loss were identified from medical records and were followed for 4 months after starting the medication during the period between (July - and December 2019). Stage 2 was ongoing during the same period to contact patients during and after the continuation of the 4-months. Liraglutide is prescribed without charge to the patient in this setting. All patients who met the inclusion criteria were contacted to be included in the cross-sectional survey. Data collected during the stage is described in section 2.3 (Survey Development and Implementation)

Population and sampling for the retrospective phase

Population

A list of all patients taking liraglutide within the hospital's obesity clinic was generated. Patients with increased fat mass and risk for cardiometabolic risk factors were referred to the obesity clinic by family medicine physicians. The obesity clinic staff includes a health educator. Before starting Liraglutide patients received focused education regarding appropriate lifestyle intervention, the drug, its side effects, and how to titrate the dose from 0.6 mg/day to reach the full dose of 3 mg/day in five weeks. Patients were either considered or not in this study according to the following criteria:

Inclusion criteria: male and female patients aged 18 years and above, who had a body-mass index (BMI) of at least 30 kg/m^2 or a BMI of at least 27 kg/m^2 with other comorbidities (Hypertension, type 2 diabetes, Polycystic ovary syndrome, Obstructive sleep apnea, nonalcoholic fatty liver/ nonalcoholic steatohepatitis, female infertility, and dyslipidemia).

Exclusion criteria: previous use of GLP1 agonists including Liraglutide 1.8 mg, and Pregnancy, patients on other obesity medications, patients on psychiatric medications or hormonal therapy.

Sample size for the retrospective phase

The sample size calculation was based on the minimum sample size required to detect a difference between pre-post observations [$n = \sigma^2 (Z_{1-\beta} + Z_{1-\alpha/2})^2/\Delta^2$] [23]. For the current study, a power of 80% ($\beta = 0.2$) was used, with a two-sided α level of 0.05 (95% confidence interval). For Δ, studies have shown that a weight reduction of 5% to 10% can provide clinically relevant improvements in obesity-related comorbidities and quality of life. Based on this, the current study aimed at a minimum of 5% reduction in weight. Concerning SD (σ), a retrospective study carried out in Saudi Arabia [17] has shown a mean weight difference of 2.32 (SD: 7.69). This was the only study retrieved investigating the effect of liraglutide on weight management. Thus, the current study used a value of SD of 8. Based on the above information, the minimum sample size required was calculated to be 20 patients. As a rule of thumb, 30 is the minimum sample size to test for normality. Because normality check was thought before analyzing the data generated, the minimum required sample was considered to be 30.

Data collection process for the retrospective phase

A list was generated from electronic medical records that included all patients who were prescribed liraglutide. Data that were collected retrospectively included age, gender, weight, and BMI at baseline and 4-month, and weight-related comorbid conditions.

Survey development and implementation

Patients were surveyed to investigate diet and exercise, medication adherence and reasons for non-adherence, and side effects experienced. Data were kept secured in Research Electronic Data Capture (REDCap). A second investigator randomly checked a sample of 10% of the data. We identified a few errors in the data during this process; therefore all data were then double-checked against the medical record.

A telephone-based survey was used to gather the required information from the study participants. The survey was prepared based on the published literature and the documented side effects of liraglutide, as one of the main objectives of this survey was to collect data on the drug tolerability. The survey consisted of three domains. The first domain involved general characteristics which included medical record number, gender, and contact details. The second domain investigated the side effects the patients experienced during the first month, second month, and the 4-month of liraglutide use, and whether participants were still using the medication. Reasons behind stopping the medication were also investigated. A list of side effects was provided which included nausea, vomiting, diarrhea, constipation, headache, and dizziness. The patients could also add any additional side effects that they experienced and they were not listed in the survey. The third domain involved information on adherence to diet and exercise during the 4 months of liraglutide use.

The instrument went through content validity by a physician from KAAUH, and an assistant professor of pharmacy practice from the College of Pharmacy, PNU. Concerning data collection, three investigators contacted, through phone, the patients to explain the study objectives and request consent. The aim of the study was clearly explained to patients before taking part in the study. Participants gave their consent before participating in the study. Participants were informed that their participation was voluntary and that they could withdraw from the study at any time. Furthermore, participants were informed that they will not be identified in any study report and that the information collected would be confidential.

Study outcomes

The primary outcome was the mean change in body weight and BMI from baseline as collected from the medical chart. The secondary outcome was the tolerability and pattern of use, defined as the continuation of the medication and/or reason for stopping, and prevalence of diet and exercise. Diet and exercise were defined as eating healthy choices and performing aerobic exercise at least 3 hours/week.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Descriptive statistics were conducted which involved frequency percentage and mean values ± SD. Paired sample t-test was used to infer the mean differences in weight and BMI at an alpha level of 0.05.

Ethical considerations

The study was approved by the Institutional Review Board at Princess Nourah bint Abdulrahman University (PNU) (H-01-R-059). The Institutional Review Board at PNU also approved the verbally informed consent process for the survey part. The data was collected and stored in concordance with the data protection act and the general data protection regulations as per the PNU. No patient identifiers were used in the report. Data confidentiality was maintained throughout all stages of the study. This study complies with the Declaration of Helsinki.

Results and Discussion

Baseline characteristics of the patients

The number of patients who met the inclusion criteria was 110, of whom; four patients were excluded because they had no documented weight or BMI at baseline. Additionally, one patient was excluded because of previous liraglutide use before follow-up with KAAUH. To meet the study objective, a minimum required sample size of 30 was calculated. However, the study enrolled 105 patients, of whom 36 (34.3%) had complete data until the fourth month of the study period. Baseline characteristics of all enrolled patients (n = 105) and those who continued using the medication until month 4 are illustrated in **Table 1**. The recruitment of study subjects is illustrated in **Figure 1**.

Table 1. Baseline characteristics of the patients

Characteristic	All patients (n = 106)	Patients who had documented data until month-4 (n = 36)
	Frequency (%)	Frequency (%)
Sex		
Male	21 (20.0%)	4 (10.1%)
Female	84 (80.0%)	32 (89.9%)

Age (years) (mean, ±SD)	41.99±12.45	44.86±11.03
Starting weight in Kg (mean, ±SD)	97.88±16.17	101.63±14.95
Starting body-mass index (Kg/m^2) (mean ±SD)	37.69±5.39	39.05±5.23
Overweight (BMI 27-29.9 Kg/m^2)	5 (4.76%)	0 (0%)
Obese (BMI) ≥ 30kg/m^2)	100 (95.2%)	36 (100%)
Weight-related comorbid conditions		
Diabetes mellitus type 2	27 (25.71%)	11 (30.5%)
Hypertension	24 (22.85%)	13 (36.1%)
Polycystic ovary syndrome	8 (7.62%)	1 (2.7%)
Obstructive sleep apnea	2 (1.90%)	2 (5.5%)
Female infertility	2 (1.90%)	2 (5.5%)
Dyslipidemia	28 (26.67%)	10 (27.8%)
Nonalcoholic fatty liver disease	1 (1.0%)	0 (0%)
None	49 (46.67%)	14 (38.9%)

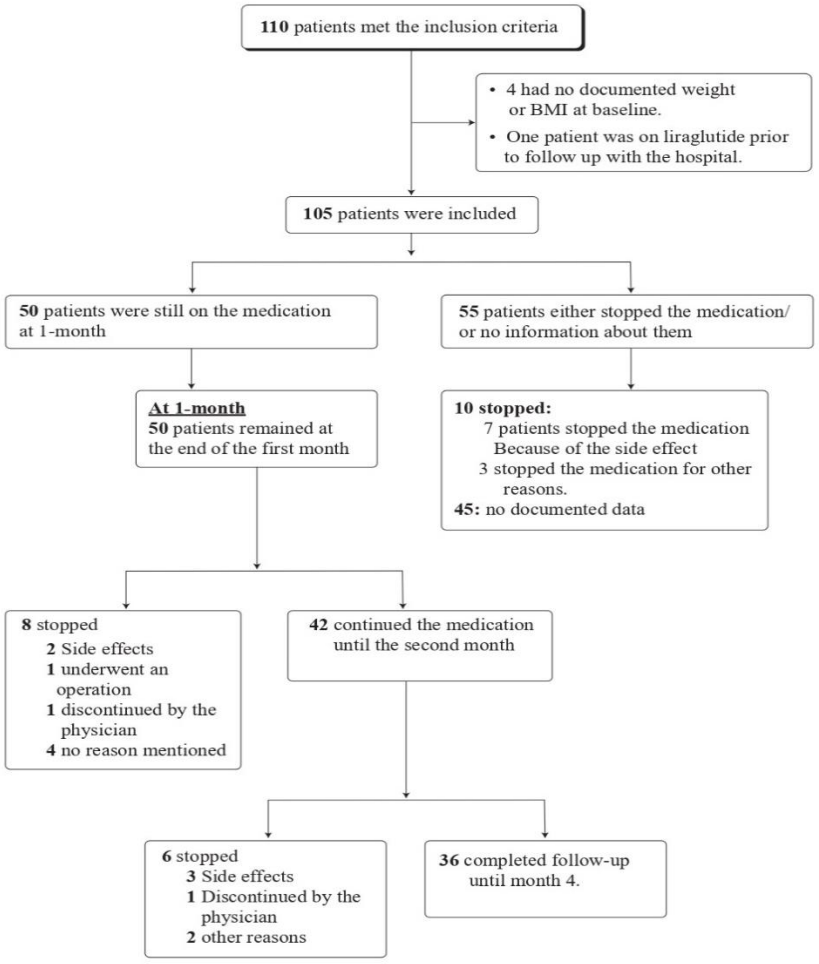
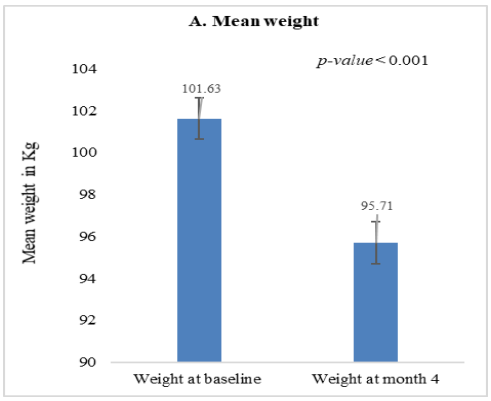


Figure 1. Flow diagram of the study

Primary outcome: change in body weight and body mass index

The analysis of the 36 patients showed that the mean ± standard deviation of body weight was 101.63±14.95 kg, and 95.71 ± 14.78 kg at baseline and month 4, respectively. The mean difference in weight was 5.92± 5.54 kg (range 4.05 – 7.80, with a *p*-value of < 0.001. The average percent change in weight from baseline was -5.76% (range 2.17% - 22.69%). Half of the patients (50%, n=18) lost ≥ 5% of their body weight, of which 33% lost greater than 10% of their body weight. Average BMI was 39.05±5.22 and 36.82± 5.49 kg/m^2 at baseline and month 4, respectively. There was a significant change in BMI from baseline (2.24 kg/m^2; range 1.56 – 2.91, p-value < 0.001). **Figure 2** illustrates the mean body weight and mean BMI at baseline and month 4.



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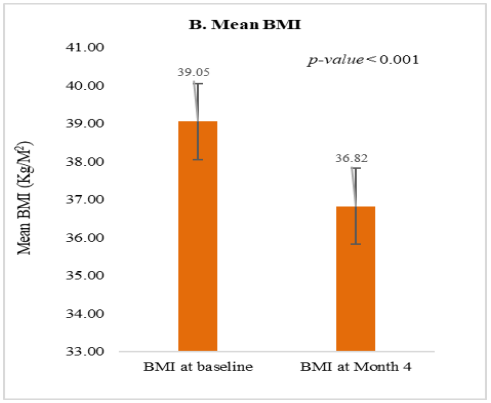

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Figure 2. Mean body weight and BMI at baseline and at 4-months for the included patients (n = 36)

Secondary outcome: pattern of use and tolerability

The results of the pattern of use and tolerability are based on the survey results. Of the 105 patients who met the inclusion criteria, 65 responded to the survey. Results of the use of liraglutide and the reasons for stopping the medication are presented in **Table 2**. Of the respondents, 55.4% remained on liraglutide during the 4 months and completed their follow-up visit. Of the patients who discontinued the medication, almost half of them reported side effects as the main reason. The findings regarding the number of patients who adhered to diet and exercise during different time points of the study period are presented in **Figure 3**. The side effects reported in month 1, month 2, and month 4 are presented in **Table 3**. These side effects included nausea, vomiting, diarrhea, headache, and dizziness.

Data on differences between the baseline characteristics of respondents (who completed the 4 months) and non-respondents show that the non-respondents appeared to be younger (age: 40.76±10.82 vs 44.86±11.03); and fewer females were identified among the non-respondents (28/40 [70%] vs 32/36 [89%]). No other significant differences in the baseline characteristics were identified between the two groups.

Table 2. The pattern of liraglutide use and the reasons for stopping the medication over the 4-month period. (n = 65)

Characteristics	Number (%)
Gender	
Male	9 (14%)
Female	56 (86)
The Use of the medication during the 4 months	
Number of patients who were on the medication up to the fourth month	36(55.4%)
patients who stopped the medication	26 (40%)
within 1 month of use	12 (18.4%)
within 2 months of use	8 (12.3%)
within 4 months	6 (9.2%)
Missing weight value at month4	3 (4.6%)
***Reasons for stopping the medication among the 25 patients**	
Side effects	12
Within 1 month	7
within 2 months of use	2
within 4 months	3
Underwent an operation	2
Discontinued by the physician	2
Other reasons	3
No reason mentioned	6

*Results are presented as numbers only as the total number of patients stopping the medication is well below 100.

Table 3. Side effects prevalence at month 1, month 2, and month 4

Side effect	At month 1 (N = 62)		At month 2 (N = 50)		At month 4 (N = 42)	
	n (%)	95% Confidence Interval For the %	n (%)	95% Confidence Interval For the %	n (%)	95% Confidence Interval For the %
Nausea	20 (32.3%)	20.9% -45.3%	15 (30.0%)	17.9% - 44.6%	6 (14.3%)	5.4% -28.5%
Headache	9 (14.5%)	6.9% -25.8%	3 (6.0%)	1.3% - 16.5%	1 (2.4%)	0.1% - 12.6%

Dizziness	6 (9.7%)	3.6% - 19.9%	5 (10.0%)	3.3% - 21.8%	2 (4.8%)	0.6% - 16.2%
Vomiting	4 (6.5%)	1.8% – 15.7%	3 (6.0%)	1.3% - 16.5%	1 (2.4%)	0.1% - 12.6%
Constipation	3 (4.8%)	1.0% – 13.5%	2 (4.0%)	0.5% - 13.7%	3 (7.1%)	1.5% - 19.5%
Diarrhea	3 (4.8%)	1.0% – 13.5%	4 (8.0%)	2.2% - 19.2%	3 (7.1%)	1.5% - 19.5%
Other side effects	9 (14.5%)	6.9% -25.8%	7 (14.0%)	5.8% - 26.7%	6 (14.3%)	5.4% -28.5%

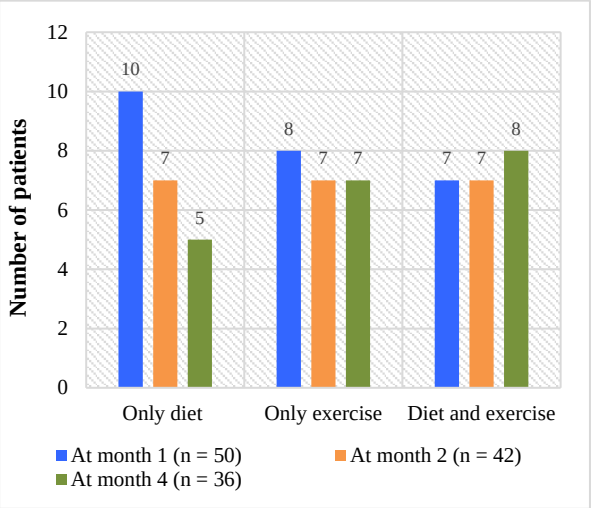

Figure 3. The pattern of diet and exercise use during the study period

This study was carried out to evaluate the effectiveness, tolerability, and pattern of use of once-daily 3 mg liraglutide, for weight management in overweight/obese patients. The study included more females than males. Around a third of the enrolled patients maintained follow-up for four months, and were enrolled in the per-protocol analysis to measure effectiveness. Results of this study indicated that treatment with Liraglutide 3.0 mg daily resulted in significant weight reduction among the studied cohort. This is in accordance with previous studies. However, the proportion of patients who discontinued the medication was high. Of the enrolled patients, almost half of them lost follow-up, and no information was reported concerning the reasons behind not following up with the clinic. The nature of the real-life study is often subjected to this type of loss to follow-up as reported in previous research about weight loss associated with liraglutide [21].

Around half of the enrolled patients responded to the cross-sectional survey. The most common reason for stopping the medication was intolerance to side effects. The patients reported side effects due to liraglutide use at different periods. These side effects included nausea, headache, dizziness, vomiting, constipation, and diarrhea. Nausea appeared in one-third of the subjects during month 1 and month 2 of liraglutide use and decreased by 50% in month 4. The majority of the side effects are not frequent, and all showed a decrease in frequency at month 4. The side effects reported here are in line with what has been published in real-life investigations [7, 18, 19] and other studt types [24, 25] Nevertheless, most of the side effects reported may not be life-threatening and might be out weighted by the benefit of liraglutide in decreasing the risk of other comorbid conditions.

A key to successful weight reduction is adherence to a healthy lifestyle as much as possible. The use of liraglutide is recommended to be accompanied by diet and exercise habits. Few patients, in the current study, reported their adherence to diet and exercise while on liraglutide therapy. The reasons behind non-adherence were not stated. To enhance weight loss, both habits remain crucial. A study by Park *et al*. [20] indicated that patients might still get meaningful weight loss without intensive lifestyle modifications. On the other hand a study reported that combining exercise and liraglutide therapy had better weight loss maintenance compared to either treatment alone [26]. The patients stopped liraglutide at different time points during the study period, and the main reason reported by the patients were side effects, in particular, the gastrointestinal tract symptoms.

The results of this study demonstrate that liraglutide treatment was associated with clinically significant weight loss and BMI reduction in the patients who completed the four months. The findings obtained here are comparable to what is reported in the few studies that investigated the benefit of liraglutide in routine practice [7, 18, 19, 22]. The percent reduction in weight reported in this study is comparable to what has been found in a study targeting patients from the Gulf region [27]. When compared to other drugs designed to treat obesity, for instance, orlistat, liraglutide was also found to be superior in weight reduction [19]. This could be an encouraging factor to continue on the medication. This study sheds light on the pattern of use and attitude of patients in real-life settings, without the obligation of being in a randomized clinical trial. This enrollment in a clinical trial following strict inclusion and exclusion criteria motivates patients to address their disease, attend appointments, and adhere to Liraglutide [28]. Further medication utilization and cost-effectiveness studies in real-world settings are needed. In addition, supportive mechanisms to enhance patient compliance with lifestyle changes and medications are needed.

Study limitations

The findings of this study should be interpreted by taking into consideration the way that some factors might affect these findings. The nature of the retrospective evaluation hinders more data to be gathered to better understand the findings. In the current study, out of the 36 patients who completed the 4 months, some patients with other comorbid conditions were on medications to treat their conditions (11 patients were using non-insulin therapy for type 2 Diabetes; 13 were on hypertension medications, and 10 were on Dyslipidemia medication). However, an in-depth investigation on how these medications might affect the results was not carried out. This may add to the

limitations of the study. Additionally, the use of per-protocol analysis for this study might overestimate the findings.

The study was conducted in only one center and involved a small number of patients. This may put some limitations when concluding the population under investigation. The side effect profile was collected retrospectively and thus might be subjected to recall bias in terms of the number of side effects that patients experience, but not the reason for stopping the medication. Some socio-economic characteristics that the study did not address (e.g., education and occupation) might have influenced the findings related to adherence to medication, diet, and exercise. Future studies should investigate the cost associated with non-adherence and ways to increase patients' adherence.

Conclusion

In this retrospective evaluation, persistent use of 3.0 mg of once-daily liraglutide resulted in clinically significant weight reduction, with no serious side effects. However, the persistent use of liraglutide was limited. Further real-world studies, on the Saudi population, with a large sample size, are warranted to investigate these findings.

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Conflict of interest: None

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Ethics statement: None

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