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Efficacy of 12 months therapy with glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on weight regain after bariatric surgery: a real-world retrospective observational study

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Abstract

Background The role of glucagon-like peptide-1 receptor agonists (GLP1-RAs) in patients with weight regain after bariatric surgery remains unclear. The objective of this study was to determine the efficacy and safety of 12 months of GLP1-RA treatment in a real-world patient population with weight regain after bariatric surgery.

Methods A single-centre retrospective observational study. Patients with post-bariatric weight regain subsequently treated with GLP1-RA were identified, and the effect on weight after 12 months of treatment was determined. Data are presented as medians (interquartile ranges) or frequencies (%), and Wilcoxon signed-rank tests and Mann-Whitney U tests were used for paired and nonpaired group comparisons, respectively.

Results Forty patients (80% female) were included in the analysis. Liraglutide (3.0 mg, daily subcutaneous injection, $n=22$) or semaglutide (1.0 mg, weekly subcutaneous injection, $n=18$) was started 74.5 (51.0, 108.3) months after surgery following a weight regain of 14.7 (10.3, 19.6)%. After 12 months of GLP1-RA treatment, a total body weight, BMI, and percentage excess body weight reduction of 10.5 (6.1, 14.7) kg, 3.7 (2.5, 5.3) kg/m^2, and 41.7 (22.1, 70.5)% were observed, corresponding to a loss of 99.3 (61.0, 135.4)% of the weight regained (P-value < 0.0001). The observed reduction in BMI was significantly lower with liraglutide than with semaglutide, 3.1 (2.0, 4.7) vs. 4.7 (3.7, 6.0) kg/m^2 (P-value = 0.04). Adverse events were reported in 13 (32.5%) patients, all of which were mild and transient.

Conclusion GLP1-RA therapy with liraglutide or semaglutide for 12 months is efficacious and safe for the treatment of weight regain following bariatric surgery.

Clinical trial number Not applicable.

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Keywords Bariatric surgery, GLP-1 receptor agonist, Liraglutide, Semaglutide, Weight regain

Background

Bariatric surgery is considered the most effective treatment for severe obesity and associated diseases, but patients frequently regain weight over time [1]. One review by King et al. reported that the median weight regain after bariatric surgery ranged from 8.2 to 23.8% of the maximum weight loss. One reason for the considerable difference in published weight regain estimates is the lack of a standardized definition [2, 3]. Expert opinions on the management of weight regain after bariatric surgery have been published and given that the underlying causes of weight regain are often multifactorial, a multidisciplinary therapeutic approach is recommended [4, 5]. Established treatments for overweight and obesity in patients without previous bariatric surgery, such as glucagon-like peptide-1 receptor agonists (GLP1-RAs), are considered therapeutic options, although this recommendation is based on a limited number of retrospective studies. It has been suggested, that GLP1-RA therapy is more effective than non-GLP1-RA-based therapies for the treatment of weight regain after bariatric surgery [6]. This is supported by several observational studies and case reports [6–12]. One RCT in postbariatric patients reporting a change in HbA1c after 26 weeks of treatment with liraglutide as the primary endpoint has been published to date and demonstrated a significant weight loss of 4.2 kg in the liraglutide arm [13]. Our group has previously reported data on the short-term efficacy of liraglutide and semaglutide in patients with weight regain after bariatric surgery, and we were able to demonstrate a loss of 67% of the weight previously regained after 6 months, with more weight lost in the semaglutide group [10]. The 12-month results from our cohort are reported in the present manuscript.

The aim of this retrospective observational follow-up study set in Switzerland was to describe the weight effect of 12 months of treatment with liraglutide or semaglutide in a real-world patient population with secondary weight regain after bariatric surgery.

Methods

Study design and participants

The study was conducted as a single-center retrospective observational study in the obesity outpatient reference center at the Cantonal Hospital of St. Gallen, Switzerland.

Physicians at the center reviewed their patient data until 02/2022 and identified patients > 18 years of age treated with GLP1-RA due to weight regain after bariatric surgery. Weight regain was defined as any weight gain after having reached the weight nadir, at least 15 months after bariatric surgery. The decision of whether and when to initiate GLP1-RA treatment and the choice of analog was made at the discretion of the attending physician based on patient-specific circumstances, including the cardiovascular risk profile and patient preferences. Liraglutide was prescribed on-label (3.0 mg, daily subcutaneous injection), and semaglutide was prescribed off-label at the starting dose approved for type 2 diabetes (T2D) (1.0 mg, weekly subcutaneous injection).

The visit when GLP1-RA treatment was initially prescribed was defined as the baseline visit. Data from the following 6- and 12-month visits were collected retrospectively from the clinical database between February and April 2022. The study was conducted in accordance with the Declaration of Helsinki. The regional ethics committee approved the study (BASEC No. 2022 – 00208), and all participating patients had signed an informed general consent form.

Outcome measures

The primary outcomes were changes in total body weight (kg) and BMI (kg/m^2), as well as the proportion of body weight regain and excess body weight lost after 12 months of GLP1-RA treatment as compared with baseline. Six-month data were also assessed. There are currently no standardized definitions of weight regain metrics after bariatric surgery. For the current study, baseline weight was defined as the total body weight at the visit when GLP-1 RA was prescribed. Weight regain was defined as any weight gain after having reached weight nadir, at least 15 months after bariatric surgery, and excess body weight was defined as body weight above an equivalent BMI of 25 kg/m^2, which is the definition commonly used in clinical practice.

The secondary outcomes included GLP1-RA-related adverse events as well as the prevalence of obesity-related comorbidities (dyslipidemia, hypertension and T2D) at baseline and at 6 and 12 months after treatment initiation. Dyslipidemia and arterial hypertension were defined as the prescription of lipid-lowering and antihypertensive medication, respectively. Relevant information was collected from the patients' medical records.

Statistical analysis

Data are presented as medians and interquartile ranges for continuous variables and frequencies and percentages for categorical variables, if not otherwise indicated. Several sensitivity analyses were performed to evaluate the influence of the GLP1-RA analog (liraglutide vs. semaglutide), magnitude of weight regain below and above the median value, prevalence of T2D, age below and above the median, sex, time between bariatric surgery and

GLP1-RA initiation below and above the median, presence of a potential anatomical cause for weight regain, and self-payer status on the results. As semaglutide was prescribed off-label and therefore not reimbursed by health insurance, the latter analysis was conducted among patients prescribed liraglutide. The Wilcoxon signed-rank test and Mann-Whitney U test were used for paired and nonpaired comparisons of continuous traits, respectively. XLSTAT (Lumivero, Denver, CO) was used for descriptive statistics, and differences in characteristics between groups were analyzed with SAS 9.4 (SAS Institute). A p-value < 0.05 was considered to indicate statistical significance.

Results

Patient selection

The participant flow chart is shown in Fig. 1. Four patients who switched from liraglutide to semaglutide and one patient on a lower dose of liraglutide (1.8 mg, daily subcutaneous injection) were excluded to limit the degree of heterogeneity in the patients analyzed.

Among the 40 patients included in the analysis, 77.5% ($n = 31$) had proximal Roux en-Y gastric bypass, 7.5% ($n = 3$) had sleeve gastrectomy, 5.0% ($n = 2$) had distal Roux en-Y gastric bypass, and 10.0% ($n = 4$) had undergone bariatric surgery twice (Supplemental Table 1). The first baseline visit took place in October 2018, and the last visit took place in April 2021. At the postoperative weight nadir, patients had lost 35.4 (29.6, 42.5) kg of total body weight, 13.0 (11.2, 15.6) kg/m^2, and 75.6 (64.9, 91.6)% excess body weight.

Patient characteristics at baseline

The median age at baseline was 50.0 (45.5, 58.5) years (Table 1), and 80% of the patients were females. Treatment with GLP1-RAs was initiated 74.5 (51.0, 108.3) months after surgery; 55.0% ($n = 22$) of the patients received liraglutide and 45.0% ($n = 18$) received semaglutide. At the time of GLP1-RA initiation, body weight and BMI were 92.0 (82.5, 104.6) kg and 32.6 (30.3, 38.9) kg/m^2, respectively, following a total body weight regain of 12.1 (8.7, 16.3) kg or 14.7 (10.3, 19.6)% of the postbariatric weight nadir, corresponding to an increase in BMI of 4.4 (2.9, 5.8) kg/m^2. The prevalence rates of T2D, dyslipidemia, and hypertension were 22.5%, 20.0% and 15.0%, respectively (Table 1). Patients receiving semaglutide tended to be older and had a higher prevalence of T2DM (Supplemental Table 3).

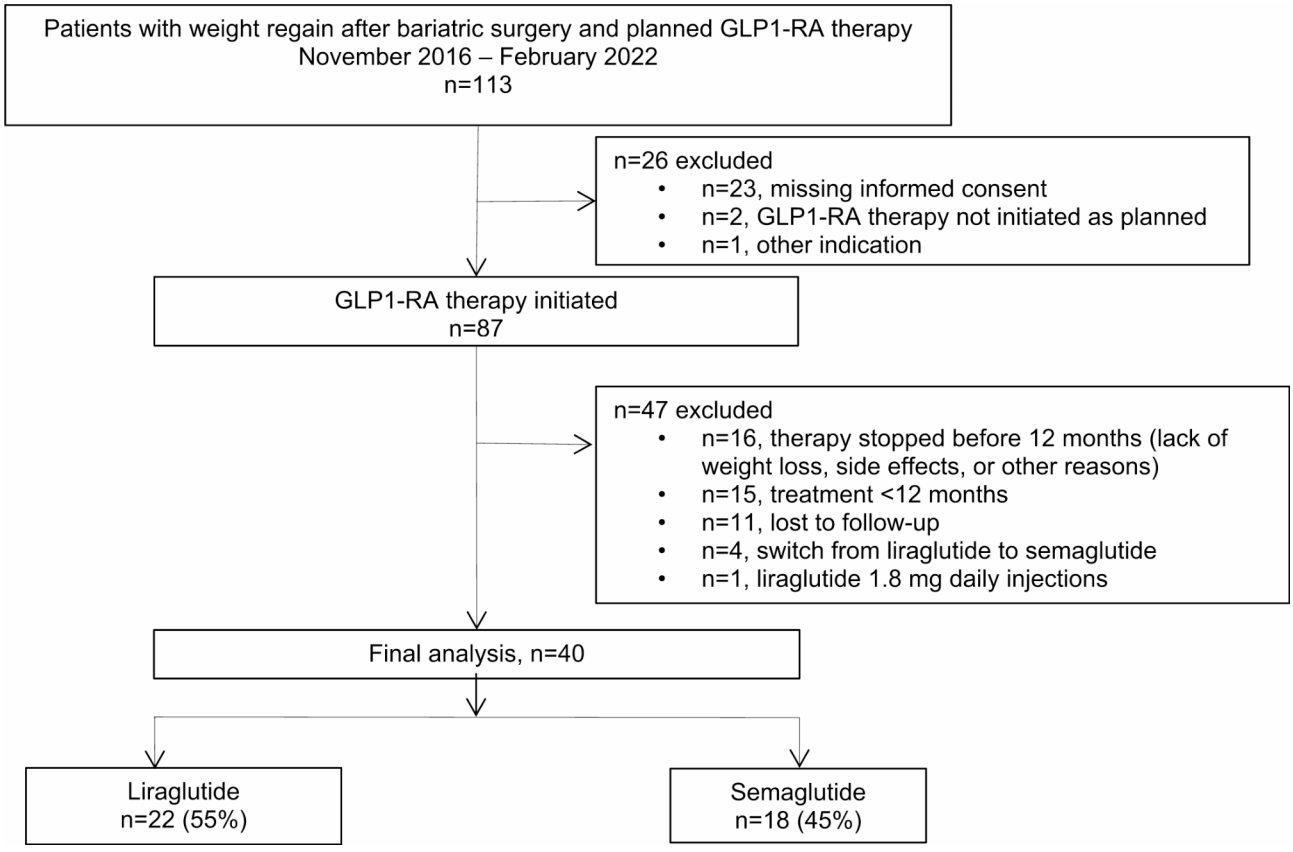

Fig. 1 Participant flow chart. GLP1-RA, glucagon-like peptide-1 receptor agonist

Table 1 Patient characteristics before bariatric surgery, at weight nadir, at initiation, 6 and 12 months of GLP1-RA treatment

Characteristics	Pre-surgery	Post-surgery weight nadir	GLP1-RA initiation	6 months treatment	12 months treatment
Age, yrs	43.0 (39.8, 52.5)	44.5 (41.0, 53.8)	50.0 (45.5, 58.5)	51.0 (46.0, 61.0)	51.5 (46.5, 59.5)
Time after BS, mo	-	17.0 (12.0, 25.3)	74.5 (51.0, 108.3)	77.0 (51.0, 108.0)	86.5 (65.0, 121.0)
Weight, kg	115.0 (106.5, 127.1)	80.9 (74.0, 89.2)	92.0 (82.5, 104.6)	81.6 (75.7, 94.4)	80.3 (73.5, 92.5)
BMI, kg/m^2	41.8 (39.6, 47.1)	29.2 (26.5, 32.2)	32.6 (30.3, 38.9)	30.7 (28.5, 35.6)	29.3 (27.1, 34.1)
T2D, n (%)	10 (25.0)	5 (12.5)	9 (22.5)	8 (24.2) [c]	9 (22.5)
HbA1c, n (%)[a]	7.4 (7.0, 8.1)	6.8 (6.5, 7.1) [b]	7.1 (6.6, 7.7) [b]	6.3 (6.3, 6.5) [d]	5.9 (5.6, 6.3) [d]
OAD, no[a]	-	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 1.3)	1.0 (1.0, 1.5)
Insulin, n (%)[a]	5 (12.5)	0	1 (11.1)	1 (12.5)	0
Dyslipidaemia, n (%)	6 (15.0)	5 (12.5)	8 (20.0)	7 (21.2)	8 (20.0)
Hypertension, n (%)	17 (42.5)	6 (15.0)	6 (15.0)	6 (18.2)	7 (17.5)

If not otherwise specified data are median values with interquartile range in brackets. Data are based on 40 patients, except at 6 months treatment ($n=33$)

BMI, body mass index; BS, bariatric surgery; HbA1c, glycated haemoglobin A1c; mo, months; No, number of; OAD, oral antidiabetic drugs; T2D, type 2 diabetes; yrs, years; [a] In patients with T2D. [b] information missing in one patient [c] information missing for seven patients [d] information missing in three patients

Changes in body weight after 12 months of GLP1-RA treatment

After 12 months of GLP1-RA treatment, 40 patients lost 10.5 (6.1, 14.7) kg, 3.7 (2.5, 5.3) kg/m^2 and 11.2 (7.4, 15.2)% of their total body weight, corresponding to 41.7 (22.1, 70.5)% of their excess weight and 99.3 (61.0, 135.4)% of their weight regained (P-value < 0.0001) (Fig. 2). Although the majority of the observed weight loss was already achieved at 6 months ($n=33$ [data from 7 patients are missing at 6 months], 7.8 [5.6, 11.4] kg and 3.0 [2.3, 3.8] kg/m^2), additional weight loss was evident between 6 and 12 months ($n=33$, 3.2 [0.4, 5.5] kg and 1.3 [0.1, 2.0] kg/m^2) (Fig. 2). A statistically significant difference in weight loss was observed between patients receiving liraglutide ($n=22$) and those receiving semaglutide ($n=18$) ((-3.1 [-4.7, -2.0] kg/m^2 vs. -4.7 [-6.0, -3.7] kg/m^2, P-value = 0.04) (Supplemental Fig. 1). The proportions of patients who achieved ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20% weight loss are shown in Fig. 3. A further stratification of the results by the GLP1-RA analog did not reveal any statistically significant differences (all P-values > 0.05).

Sensitivity analyses

A statistically significant difference in the magnitude of weight loss following 12 months of treatment was observed when accounting for time between bariatric surgery and GLP1-RA initiation (< 74.5 months [$n=20$] or ≥ 74.5 months [$n=20$], -3.2 (-6.9, 0.38) kg/m^2 vs. -5.0 (-14.2, -0.29) kg/m^2, P-value = 0.04) (Supplemental Fig. 2). No other significant differences were observed in the stratified analysis (Supplemental Figs. 3–8, all P-values > 0.05).

Changes in obesity-related comorbidities after 12 months of GLP1-RA treatment

At baseline, nine patients (22.5%) were diagnosed with T2D. A reduction in HbA1c at 12 months compared with baseline was observed among six of the seven patients with data available at both time points (6.1 [5.8, 6.4]% vs. 7.4 [6.6, 7.8]%, P-value = 0.047). One patient treated with insulin at baseline was still on insulin after six months of treatment but was free of insulin at 12 months (with unchanged OAD treatment). Two patients had reduced anti-diabetic treatment to one instead of two OADs. Overall, no difference in the proportion of patients prescribed lipid-lowering medication was observed, and one more patient was treated for hypertension.

Reported side effects of GLP1-RA treatment

Adverse events were reported in 32.5% ($n=13$) of the patients, all of which were mild and transient (Supplemental Table 2). Adverse events tended to be more frequently reported among patients receiving semaglutide than among those receiving liraglutide (44.4% vs. 22.7%, P-value = 0.14). The observed difference was driven primarily by more patients reporting constipation (22.2% vs. 4.5%, P-value = 0.09), although none of the observed differences reached statistical significance.

Discussion

The 40 patients with postbariatric weight regain included in this retrospective observational study that continued GLP1-RAs for 12 months almost entirely lost the previously regained weight (99.3 [61.0, 135.4]%), with greater weight reduction observed among patients treated with semaglutide than in those treated with liraglutide. Although the retrospective nature of the study does not

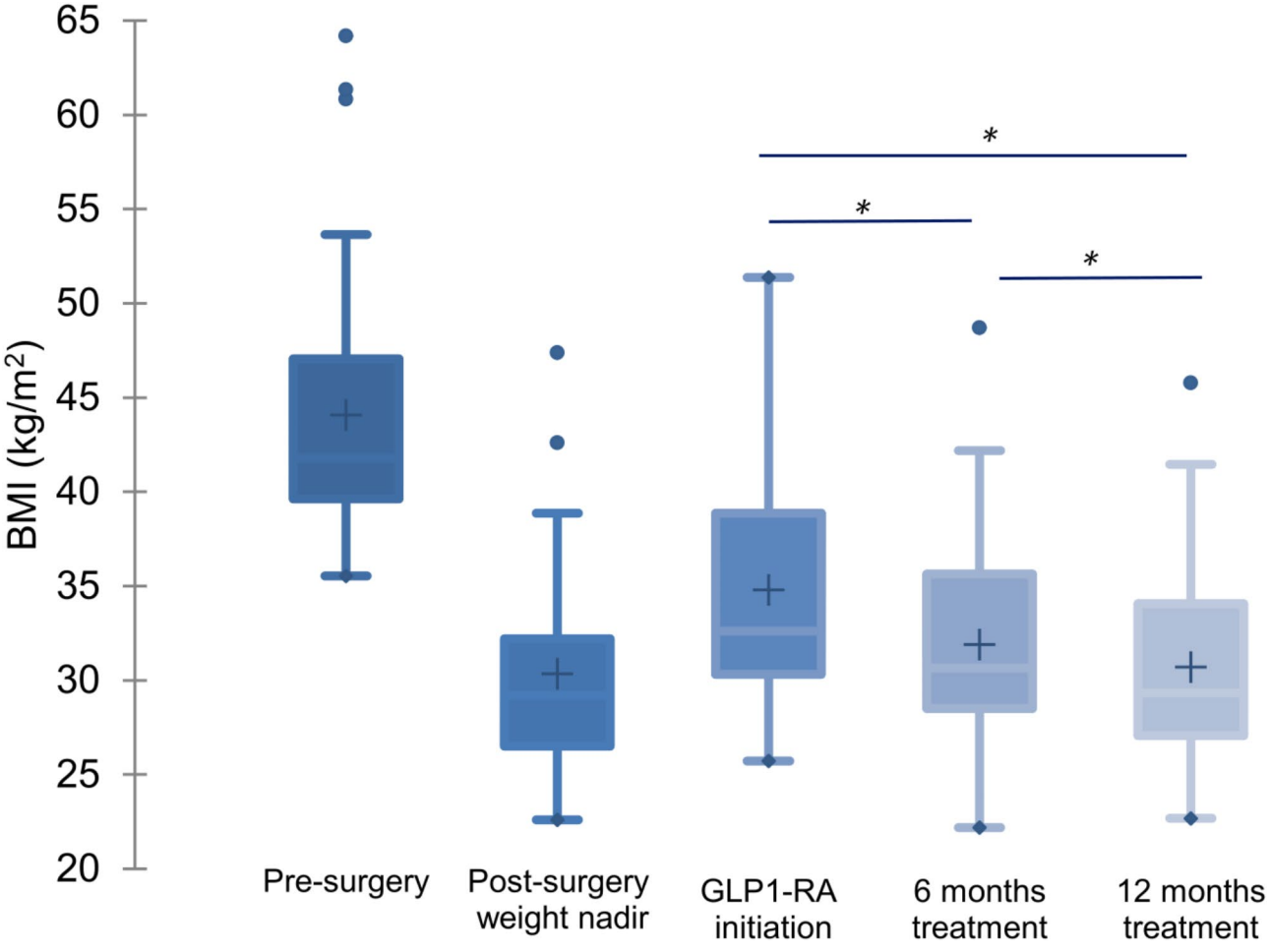

Fig. 2 Box plot showing the distribution of BMI before bariatric surgery, at weight nadir, at the time of GLP1-RA initiation, and at 6 and 12 months of GLP1-RA therapy ($n=40$, except at 6 months [$n=33$]). GLP1-RA, glucagon-like peptide-1 receptor agonist; BMI, body mass index. * *P*-value < 0.0001 based on paired nonparametric tests (Wilcoxon signed-rank test)

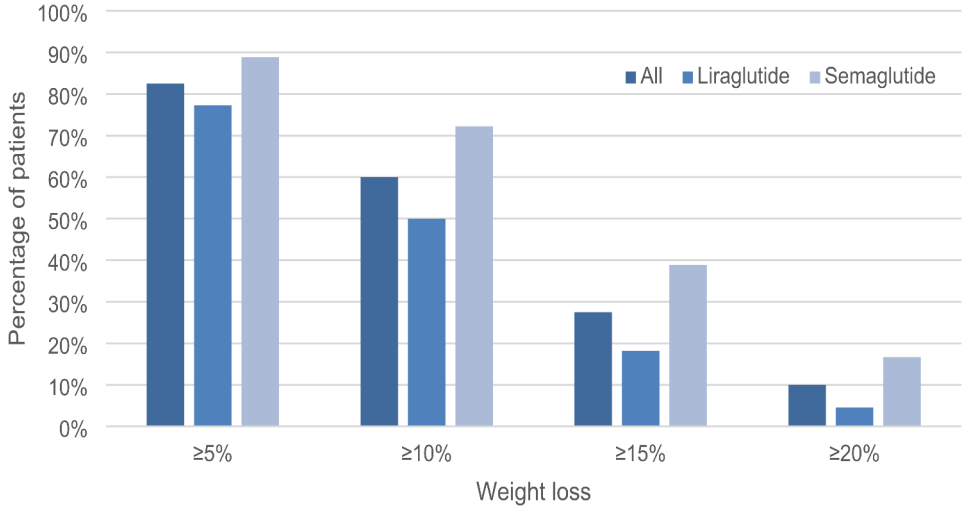

Fig. 3 Histogram showing the proportion of patients with ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% weight loss following 12 months of GLP1-RA treatment overall and stratified by analog ($n=40$). GLP1-RA, glucagon-like peptide-1 receptor agonist

allow us to draw firm conclusions, considering the number of patients who were initiated on GLP1-RAs during the observed time window, our data suggest that this superb response may be expected in at least 45% of treated patients (40/87). In line with previous findings, adverse events were relatively rare and all were mild and transient [14, 15].

The weight loss of 11.2% observed in the current study in 40 patients, 22.5% of whom had T2D, is in line with previous studies in postbariatric patients with weight regain given GLP1-RA therapy for 12 months. In Gazda et al., a weight loss of 8.9% was obtained with all available GLP1-RA-based therapies without further specification in 33 patients, of whom an unknown proportion had T2D [6]. Lautenbach et al. reported weight loss of 14.7% with semaglutide in 29 patients without T2D, and Murvelashvili et al. reported weight loss of 8.8% with liraglutide and 12.9% with semaglutide in a total of 207 patients, 7.7% of whom had T2D [6, 11, 12]. The proportion of patients with T2D is relevant, since weight loss following GLP1-RA therapy is usually greater in patients without T2D [14–17]. Since in our study, patients with T2D were more likely to receive semaglutide, this might have underestimated the magnitude of the superior weight loss effect observed as compared to liraglutide. Furthermore, the observed superior effect of semaglutide over liraglutide is in line with a recent meta-analysis based on randomized clinical studies [18] and is further supported by the results of Murvelashvili et al. [12]. That semaglutide was used off-label at a lower dose approved for diabetes management implies that the observed beneficial effects in terms of weight reduction are likely underestimating the expected effect of the higher 2.4 mg dose that is currently available for weight maintenance.

In the present study, a significantly greater weight loss was observed when GLP1-RA was initiated ≥ 74.5 months postsurgery. This could be explained by waning of the initial hormonal changes after bariatric surgery, which include elevations in postprandial GLP-1 levels [19]. Lower levels of endogenous GLP-1 would allow for exogenous stimulation of GLP-1 receptors with a GLP1-RA to have a greater effect on weight. However, knowledge on the mechanisms leading to postbariatric weight regain is limited and other yet to be identified mechanisms may account for our finding [19].

A weight loss of 10–15% has been shown to have a major beneficial effect on obesity-related complications such as T2D, dyslipidemia, hypertension, hepatic steatosis and obstructive sleep apnea. In the present study, an improvement in HbA1c was observed among patients with T2D. Although not statistically significant, likely due to the small number of patients, the general trend is supported by the observed changes in antidiabetic treatment. The number of patients with more than one oral antidiabetic medication was reduced by one, and the one patient with insulin therapy at the time of GLP1-RA initiation was free of insulin. That 60% and 30% of the patients in the current study achieved ≥ 10% and ≥ 15% weight loss, respectively, with a greater reduction in weight seen with semaglutide, further supports GLP1-RA as a therapeutic option to reduce long-term cardiovascular risk and improve the overall health in patients with weight regain after bariatric surgery.

Although the majority of weight loss observed in the current study occurred during the first 6 months of treatment, patients continued to lose weight throughout the entire 12-month period. This is in line with a plateau effect usually being established at approximately 12–18 months of treatment [14–17]. The long-term efficacy of semaglutide for weight management for up to four years has been confirmed in non-bariatric obese patients and treatment withdrawal leads to substantial and rapid weight regain [20, 21]. This underlines that obesity is a chronic condition requiring long-term or even lifelong multimodal management, including nutritional and behavioral counselling, and medical and surgical therapy in many patients. The recently introduced concept of a more phenotype-directed pharmacological obesity management remains to be translated to a real-world setting and the postbariatric situation [22].

Considering the continued rise in the prevalence of obesity, the need and demand for pharmacological agents for weight maintenance could cause significant challenges with respect to availability (as currently seen with semaglutide), and cost benefits. In nonbariatric patients, some experts even recommend a staged approach with initial GLP1-RA therapy for 12–18 months until maximal weight loss is achieved, after which weight loss therapy should be stopped and replaced by lifestyle counseling, with the option of a temporary booster therapy with a weight loss drug in case of significant weight regain [23]. Issues, such as real-world costs, tolerability and access, especially in long-term therapy, will remain a challenge for clinical practice and health systems [23].

Adverse events were mentioned in the patient records of every third patient, all of which were transient in nature. The majority were related to the gastrointestinal system with nausea reported most frequently. No serious adverse events were reported, as was partly expected given the study design. The frequency and nature of the reported mild and transient adverse events are consistent with previous study findings [7, 18]. However, the observed number of patients who discontinued GLP1-RA therapy is a cause of concern. Almost 20% of the identified patients who initiated GLP1-RA stopped treatment within the first 12 months, the majority due to undesired side effects or a lack of effect. An even higher rate of discontinuation was reported in a recently published study

based on U.S. pharmacy and medical claims data during 2021. Only 27% of the 4255 patients without diabetes that were prescribed GLP1-RA for weight loss were still on treatment one year later [24]. Although the reasons for discontinuation are plentiful, this reality presents a real challenge for the medical field. Given that GLP1-RAs are among the most effective weight loss drugs currently available, this highlights the important role of the dual and triple agonists that are becoming increasingly available or are currently undergoing clinical trials in providing more treatment options. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP1-RA, has shown promising effects on weight reduction [25, 26]. In a recent retrospective analysis of 115 patients from Kuwait with weight regain after sleeve gastrectomy, significantly greater weight loss after 6 months therapy with tirzepatide than with semaglutide was observed (15.5% vs. 10.3%, P-value < 0.05) [27]. A phase 2 study of diabetes management in nonbariatric patients coadministered cagrilintide and semaglutide reported a weight loss of 15.6% kg in 32 weeks [28]. A 36-week phase 2 study of retatrutide, a GIP, GLP-1 and glucagon receptor agonist for T2D management reported a weight loss of 16.9% [29].

This study has several limitations. As a retrospective observational study there is a risk of bias and confounding due to both lack of randomization and a control group. Selection bias likely exists as only 40 of the 87 patients that initiated GLP-1 RAs had ≥ 12 months data available for the analysis. Another limitation is the off-label use of a lower semaglutide dose intended for diabetes management, which has likely underestimated the magnitude of weight loss that would have been achieved with a higher semaglutide dose, which at the time of observation period was not yet available in Switzerland. In addition, the small number of patients included limits statistical power.

A strength of the study is the real-world clinical setting, where the findings are more likely to reflect the results expected in daily clinical practice, in contrast to results from well-controlled RCTs, which often lack generalizability. To the best of our knowledge, this study is the second to investigate the effects of both liraglutide and semaglutide over a 12-month period in this patient population, the other being Murvelashvili et al. [12].

Conclusions

Although bariatric surgery remains the single most effective measure for weight control in individuals with obesity, a substantial portion of patients will require additional therapies to maintain its effects on body weight control. The reported results support that GLP1-RAs are an efficacious and safe option for the treatment of weight regain after bariatric surgery. Prospective randomized clinical trials with longer follow-up periods are urgently needed to determine the optimal medical approach for postbariatric patients with secondary weight regain.

Abbreviations

GLP1-RA	Glucagon-like peptide-1 receptor agonist
T2D	Type 2 diabetes
BMI	Body mass index
BS	Bariatric surgery
HbA1c	Glycated hemoglobin A1c
Mo	Months
No	Number of
OAD	Oral antidiabetic drugs
Yrs	Years

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01913-4.

Supplementary Material 1

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Author contributions

ABJ and UM contributed equally to this study, both in the analysis and interpretation of the data, and in writing the manuscript. All authors read and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The regional ethics committee (*EKOS Ethikkommission Ostschweiz*, St. Gallen) approved the study (BASEC No. 2022 – 00208), and all participating patients had signed an informed general consent form.

Consent for publication

Not applicable.

Competing interests

Anders B Jensen is a previous employee (2008-2010) of Novo Nordisk A/S. None of the other coauthors have any competing interests to declare.

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