Article

Impact of Treatment with GLP1 Receptor Agonists, Liraglutide 3.0 mg and Semaglutide 1.0 mg, While on a Waiting List for Bariatric Surgery

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Abstract: Background: Weight loss before undergoing metabolic and bariatric surgery (MBS) has been suggested to reduce perioperative complications, although with controversial results. The objective of this study is to evaluate the impact of treatment with GLP1-R agonists (liraglutide 3.0 mg and semaglutide 1.0 mg) on preoperative weight loss and patients' decisions regarding MBS while on a surgical waiting list. Materials and methods: One hundred and two patients on a waiting list for MBS started treatment with GLP1-RA for at least 6 months. Changes in weight at 26 and 52 weeks, the number of patients achieving >5% weight loss, and patients' decisions regarding MBS were evaluated. Results: After 52 weeks, patients lost 16.9 ± 7.2% of weight with semaglutide 1.0 mg and 16.1 ± 5.8% of weight with liraglutide 3.0 mg. All patients lost ≥5% of initial weight, 84.7% lost ≥10%, 54.6% lost ≥15%, and 27.5% reached ≥20%. A total of 68.6% of participants were satisfied with the achieved weight loss and withdrew from the waiting list for MBS. A threshold of >15.1% weight loss had the greatest sensitivity and specificity for the final decision regarding undergoing MBS. Conclusions: Losing >15% of initial weight after 52 weeks of treatment with liraglutide 3.0 mg or semaglutide 1.0 mg during the waiting list for MBS impacts patients' decisions regarding the final acceptance or rejection of the procedure.

Keywords: severe obesity; bariatric surgery; liraglutide; semaglutide; waiting list

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1. Introduction

Metabolic and bariatric surgery (MBS) has been proven to be a safe and effective treatment for severe obesity (BMI > 35 kg/m^2) and its associated comorbidities and all-cause mortality [1]. Moderate weight loss (5–10%) is enough to achieve a significant improvement in accompanying cardiovascular risk factors, but sustained weight loss is one of the greatest challenges in the management of obesity [2].

Numerous healthcare insurance plans call for a minimum of 5–15% weight loss before undergoing MBS to provide financial coverage in their attempt to limit the indications and reduce access to bariatric procedures. However, there are no randomized clinical trials, prospective studies, or meta-analyses that support preoperative weight loss as an essential prerequisite. In fact, the 1991 NIH Consensus Statement on the Treatment of Obesity [3] did not suggest the need for weight loss prior to undergoing MBS. In addition, the authors of the Updated Position Statement on Insurance Mandated Preoperative Weight Loss Requirements of the American Society for Metabolic and Bariatric Surgery (ASMBS) [4] considered this preoperative requirement arbitrary, discriminatory, and without scientific

evidence, which only leads to delaying an effective surgical approach for the management of obesity and its life-threatening comorbid conditions. Indeed, the attrition rate may be high and entails more risks than benefits.

However, there have been studies that have attempted to evaluate the potential impact of acute preoperative weight loss on perioperative and postsurgical outcomes, including the reduction in liver volume, intraoperative bleeding, anastomotic leakage, deep infections, mean hospital stay or postsurgical complications, or even trying to evaluate its utility as a predictor of surgical success. In this regard, data derived from systematic reviews and meta-analyses conclude that preoperative weight loss may have a modest impact on perioperative issues, but there is no clear evidence supporting the effectiveness of several different weight loss intervention programs on long-term postoperative weight loss [5,6]. Moreover, highly experienced surgical teams that use advanced technology, such as laparoscopic and robotic-assisted approaches, have such low complication rates that the beneficial effect of preoperative weight loss to reduce postoperative complications becomes almost insignificant [7].

Pharmacological treatment for obesity has been mainly focused on the setting of insufficient or inadequate postsurgical weight loss, weight plateau, or post-surgical weight regain [8–10]. In this regard, GLP1 receptor agonists have been the In this regard, GLP1 receptor agonists have been one of the most frequently evaluated drugs for weight treatment, but data are limited to small retrospective and observational studies with short-term follow-up (less than 6 months), reaching 3.4–9.7% weight loss, depending on the dose used [11–15]. In the few studies that followed up patients for up to 12 months, mean weight loss reached 14–17% [16–18]. The only randomized clinical trial comparing liraglutide 3.0 mg versus a placebo, after weight regain, was carried out in 70 patients with poor weight response following gastric bypass or sleeve gastrectomy and a follow-up of 24 weeks. The results showed that liraglutide 3.0 mg was better than the placebo in achieving weight loss: $-8.82 \pm 4.94\%$ vs. $-0.54 \pm 3.32\%$; $p < 0.001$ [19]. Overall, the results have proven to be similar to real-world studies in patients who have not undergone prior bariatric surgery [20–22].

Data regarding the use of anti-obesity drugs for the preoperative management of patients are rather limited. There are studies with orlistat 60 mg three times per day, sibutramine, topiramate–fluoxetine combinations, and extended-release phentermine–topiramate, attempting to achieve 10% weight loss prior to bariatric surgery [23–25], but to our knowledge, and to date, GLP1 receptor agonists have not been specifically evaluated for this preoperative indication. The European Medicines Agency (EMA) has authorized the commercialization of the GLP1 receptor agonist liraglutide 3.0 mg for patients with obesity, and semaglutide 0.25, 0.5, and 1 mg and dulaglutide 0.75 and 1.5 mg for patients with obesity and type 2 diabetes. Semaglutide 2.4 mg has been also approved by the EMA for the treatment of obesity, but its commercialization is still to come.

The objective of our study is to analyze the effect of liraglutide 3.0 mg and semaglutide 1.0 mg on preoperative weight loss in MBS candidates awaiting the procedure, as well as to evaluate the impact of pre-surgical weight loss on patients' final decisions regarding acceptance or rejection to undergoing surgery.

2. Materials and Methods

2.1. Study Design

We performed a single-center retrospective observational study. The study was approved by the Ethics Committee of the Hospital Clínico San Carlos (code: 23/581-O_M_NoSP), and is in compliance with the Helsinki Declaration.

2.2. Subjects

During the years 2019–2022, 102 consecutive patients with severe obesity (BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with associated comorbidities), aged 18–65 years, eligible for MBS, who were scheduled for the procedure with a waiting list of more than 12 months,

were offered the possibility of initiating pharmacological treatment during their waiting time in an attempt to improve potential obesity-related comorbidities until the surgical procedure was performed. Specifically, patients with type 2 diabetes were prescribed semaglutide 1.0 mg weekly, according to product label and public healthcare system funding. For individuals with obesity and no type 2 diabetes, liraglutide 3.0 mg daily was offered according to the product label, but because this treatment has no public healthcare grant, only patients who could afford a minimum 6-month treatment were included. Patients underwent the same treatment and follow-up as obese patients who were not eligible for MBS, thus resembling an approximation to a real-world study.

2.3. Treatment and Follow-Up

Participants with liraglutide 3.0 mg were instructed to dose escalate, starting with 0.6 mg once daily and increasing by 0.6 mg weekly until 3.0 mg was reached at week 5 or 6, depending on gastrointestinal tolerance. Similarly, individuals on semaglutide 1.0 mg were instructed to begin with a 0.25 mg weekly dose, and progressively titrate it after four weeks until 1.0 mg per week was reached at week 12. If after 3 months of treatment with the maximum tolerated dose a minimum 5% weight loss was not reached, treatment was withdrawn, according to the product label and indications. We did not include in our study patients who, once GLP1-RA was started, required adding another hypoglycemic agent potentially affecting weight (such as SGLT2-I, pioglitazone, or insulin) after inclusion in the study in order to avoid bias regarding the evaluation of GLP1-RAs' efficacy. At each visit, a healthcare professional recorded any possible adverse effects and verified the titration of the drugs.

In parallel, all participants received lifestyle counseling (from qualified health care professionals) every 4–6 weeks, in person or by telephone, to improve adherence. Participants were prescribed a reduced-calorie diet (−600 kcal/d deficit relative to estimated energy expenditure calculated at week 0) and increased physical activity (>150 min/wk, such as brisk walking and strength exercises). Both diet and activity were recorded daily in a diary and were reviewed during counseling visits.

After 12 months of pharmacological treatment, when the waiting time for bariatric surgery came to an end, patients were offered to choose one of three options: (1) continue pharmacological treatment and withdraw from the bariatric surgery waiting list; (2) continue pharmacological treatment and reconsider undergoing surgery later on; or (3) withdraw pharmacological treatment and undergo bariatric surgery.

2.4. Main Outcomes and Measures

Co-primary endpoints were a percentage change in body weight from baseline to week 52 and an achievement of weight loss of at least 5% of baseline weight at weeks 26 and 52. Body weight was measured using a weighing scale (SECA 684), with participants wearing light clothes and no shoes, and rounding to the nearest 0.1 kg. The percentage of body weight loss was calculated as 100 × [(body weight at baseline − body weight at week 26 or 52)/body weight at baseline].

Metabolic secondary outcomes included change from baseline in glycemic indices (fasting glucose, insulin, HOMA-IR, and hemoglobin A1c), lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, non-HDL cholesterol, and triglycerides), and hepatic function (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT)).

2.5. Statistical Analysis

Continuous variables were summarized as mean ± standard deviation. Categorical variables were expressed as absolute frequencies (percentages). The Shapiro–Wilk test was used to check the normality of the variable's distribution. Comparison between continuous variables was performed using an independent-sample *t*-test. For variables with a skewed

distribution, the Mann–Whitney U-test was used for mean comparisons. The chi-squared test was used to analyze categorical data.

Repeated-measures ANOVA was conducted for each outcome using time (moment of assessment) as a within-subjects factor and group (semaglutide vs. liraglutide) as a between-subjects factor. For the moment of assessment, only baseline, 6-month, and 12-month evaluations were included due to the presence of missing values in the visits at 3 and 9 months. Mauchly's test was used to determine whether the assumption of sphericity was met, and Leven's test was used to assess the homogeneity of variance. When a violation of sphericity was observed, Greenhouse–Geisser-corrected *p*-values were reported.

The change in laboratory variables in the whole sample was compared using the Wilcoxon signed-rank test.

Receiver operating characteristic (ROC) curves were calculated to evaluate the capacity of detecting patients who rejected bariatric surgery after pharmacological treatment. Youden's index (YI) was estimated to evaluate the best cutoff points.

A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM® SPSS 26.0, JASP Team (2023, version 0.17.1 computer software) and Jamovi (version 2.4.).

3. Results

3.1. Characteristics of the Sample

One hundred and two patients were included. The mean age was 52.88 ± 10.38 years, and 71 (69.3%) patients were women. A total of 35 patients were treated with semaglutide 1.0 mg, and 67 were treated with liraglutide 3.0 mg. As expected, the frequency of T2D was higher in the semaglutide group than in patients taking liraglutide (100% vs. 0%, $X^2 = 86.07$, $p < 0.001$).

The main clinical and demographic characteristics are depicted in Table 1 for the whole sample and each therapeutic group. There were no statistically significant differences in weight and BMI at baseline. However, the semaglutide group was older and showed a higher prevalence of arterial hypertension and dyslipidemia. Other comorbidities, such as obstructive sleep apnea and knee osteoarthritis, showed no significant differences.

Table 1. Demographic characteristics, comorbidities, and laboratory tests at baseline and according to the type of pharmacological treatment received (semaglutide 1.0 mg or liraglutide 3.0 mg).

Characteristics	Semaglutide 1.0 mg (n = 35)	Liraglutide 3.0 mg (n = 67)	Statistic (*p*-Value)
Age, years	57.22 ± 5.79	50.61 ± 11.50	3.19 (0.002) [a]
Sex, female (%)	60.0	74.62	2.32 (0.127) [b]
Body weight, kg	117.77 ± 13.80	119.60 ± 29.47	−0.34 (0.729) [a]
BMI, kg/m^2	43.05 ± 4.25	43.92 ± 8.14	−0.58 (0.557) [a]
BMI 35–39.99 n (%)	10 (28.6)	24 (35.8)	0.661 (0.719) [b]
BMI 40–44.99 n (%)	15 (42.9)	24 (35.8)	
BMI ≥ 45 n (%)	10 (28.6)	19 (28.4)	
Comorbidities			
Arterial hypertension (%)	77.1	38.80	13.53 (<0.001) [b]
Dyslipidemia (%)	54.28	31.3	5.07 (0.024) [b]
Obstructive sleep apnea (%)	28.57	17.91	1.54 (0.214) [b]
Knee osteoarthritis (%)	22.85	22.38	0.003 (0.957) [b]

Table 1. *Cont.*

Characteristics	Semaglutide 1.0 mg (n = 35)	Liraglutide 3.0 mg (n = 67)	Statistic (*p*-Value)
Laboratory tests *			
Glycemia (mg/dL)	133.96 ± 43.40	100.70 ± 13.89	1221 (<0.001) [c]
HbA1c (%)	6.82 ± 1.48	5.61 ± 0.54	1194 (<0.001) [c]
Insulin (µUI/mL)	26.07 ± 12.76	20.27 ± 14.95	578 (0.031) [c]
HOMA-IR	8.26 ± 4.86	5.22 ± 4.10	613 (0.007) [c]
Total cholesterol, mg/dL	167.53 ± 47.36	191.55 ± 43.05	572 (0.074) [c]
Non-HDL cholesterol	119.68 ± 44.73	141.46 ± 40.55	587 (0.099)[c]
HDL-c, mg/dL	47.84 ± 8.99	50.08 ± 12.67	639 (0.261) [c]
LDL-c, mg/dL	92.12 ± 36.89	114.17 ± 34.94	499 (0.020) [c]
Triglycerides, mg/dL	155.96 ± 99.69	134.40 ± 59.83	809 (0.573) [c]
AST, U/L	24.25 ± 9.63	24.27 ± 13.10	797 (0.653) [c]
ALT, U/L	26.81 ± 15.22	26.02 ± 19.76	829 (0.441) [c]
GGT, U/L	37.87 ± 22.51	34.74 ± 34.83	943 (0.057) [c]

[a]: Student's *t*; [b]: X^2-squared; [c]: Mann–Whitney's U. * Laboratory tests were available in a subgroup of 77 patients.

3.2. Efficacy of Pharmacological Treatment

Eighty-five (83.3%) participants completed 52 weeks of therapy. For the variable of weight, time-by-group interaction was not significant ($F(1,83) = 0.437$, $p = 0.582$). A significant main effect of time was observed ($F(1,83) = 328.189$, $p < 0.001$). The mean observed change in the percentage of weight loss is shown in Figure 1. The mean change in percentage weight loss at 52 weeks was 16.99 ± 7.17 for semaglutide 1.0 mg and 16.01 ± 5.77 for liraglutide 3.0 mg ($t = 0.644$, $p = 0.522$).

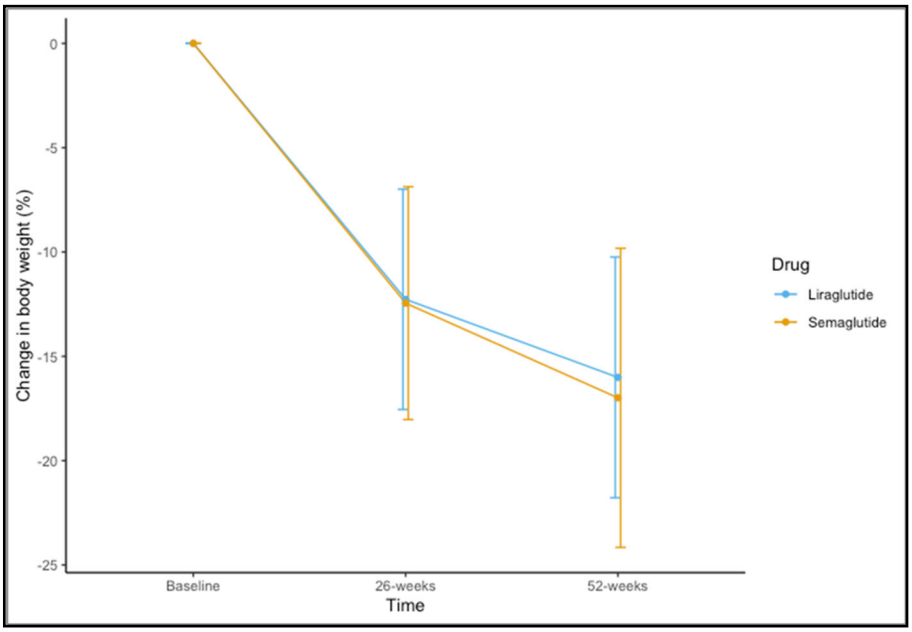

Figure 1. Changes in percentage of weight loss at 26 and 52 weeks for liraglutide and semaglutide.

When categorizing the percentage of weight loss achieved at 52 weeks, 100% of patients lost ≥5%, 85.1% lost ≥10%, 54.1% lost ≥15%, and 27.5% lost ≥20%. There were no differences between treatments ($X^2 = 1.105$, $p = 0.576$) (Figure 2).

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