



# Effectiveness, Safety and Therapeutic Adherence of Weekly Subcutaneous Semaglutide for Weight Management in Real Practice: An Observational Study

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## Abstract

**Aims:** To evaluate in a real practice setting effectiveness, safety and adherence to weekly subcutaneous semaglutide for weight reduction, along with diet and lifestyle modifications in obese/overweighted patients attending an Obesity Unit.

**Materials and Methods:** In a retrospective study, 367 patients (mean age 50.25 years, 78.36% female, mean baseline body mass index 32.39 kg/m<sup>2</sup>) were followed for 10.7 months (median) after initiation of semaglutide. Up to 24.25% of patients were previously on GLP-1 analogue therapy (mostly liraglutide) and 36.26% used background oral medication for weight loss.

**Results:** At final office visit patients averaged a weight loss of 7.97±3.42 kg (9.13±3.86% baseline body weight) and 88.07% and 30.27% of patients had achieved a≥5% and ≥10% weight loss, respectively, as compared to baseline body weight. Up to 61.19% and 33.46% of patients maintained 0.5 and 1.0 mg dose, respectively and 86.18% of patients persisted on sc semaglutide by last office visit. Nausea and abdominal pain were reported by 12.53% of patients with no severe adverse events. Background anti-obesity medication did not affect weight loss and patients on previous GLP-1 analogue therapy lost 1.43 kg less than naïve patients (p<0.001).

**Conclusions:** Out-of-label weekly administration of sc semaglutide 0.5 to 1.0 mg resulted in a significant, safe and affordable weight loss in a pragmatic setting without reimbursement of treatment cost. Magnitude of weight loss and safety profile was in line with preliminary data from a phase 2 trial, although this will need to be confirmed by an ongoing phase 3 development programme.

**Keywords:** Observational Study; Obesity Therapy; GLP-1 Analogue; Semaglutide; Appetite Control Antiobesity Drug

## Introduction

Obesity has become a major public health issue worldwide, and its prevalence is growing so uncontrolled that over the past 20 years, the rate of obesity has risen three-fold and is affecting more than 30% of population in some European countries [1]. Major health institutions recognize now obesity as a complex, multifactorial condition [2,3], associated to a number of comorbidities, including metabolic, mechanical and mental health complications that significantly impact both quality of life [4,5]

and life expectancy of affected population [6]. On the other side, treatment cost of complications derived from obesity represents a formidable burden for health public systems in many countries [7,8]. Conversely, a weight loss of 5-10% of body mass reduces obesity-related complications and improves quality of life [9,10], although this goal is difficult to achieve and maintain only with diet and lifestyle interventions [11,12]. Few safe and effective drugs are currently available for the treatment of obesity. Among

them, glucagon-like peptide 1 (GLP-1) receptor agonists have proven a combined effect on glucose metabolism and reduction in body weight associated to favourable outcomes in patients with type 2 Diabetes and coexisting obesity, including reduction of cardiovascular events for some of them [13-15].

Liraglutide, a once daily administered GLP-1 analogue was initially approved for treatment of patients with type 2 Diabetes at a dose of 1.2 to 1.8 mg, and subsequently gained approval for weight reduction in many countries, at a maximum daily dose of 3.0 mg, in combination with diet and lifestyle modifications [16-17]. Subcutaneous (sc) semaglutide, a longer-acting GLP-1 analogue was approved in Spain in 2019 for treatment of type 2 Diabetes with a weekly administration of 0.5 or 1.0 mg, and conditions for reimbursement by Spanish public health system include coexistence of obesity. Both drugs have proven clinically significant weight reductions in obese patients without type 2 Diabetes and a clinical development program is currently undergoing aiming to gain indication for sc semaglutide in weight management [18-19]. In this observational retrospective study, performed under real practice conditions, we aimed to evaluate effectiveness, safety and adherence to weekly administration of sc semaglutide in a non-reimbursed setting in patients with obesity or overweight attending an Obesity Unit in a private institution in Mallorca (Spain), along with dietary and lifestyle recommendations.

## Patients and Methods

In this retrospective study, patients attending our Obesity Unit who started on sc semaglutide since May 2019 were consecutively invited to take part in the study and after giving written informed consent, were included for analysis. Inclusion criteria were patients 18-year-old or older, with a body mass index (BMI) >25 kg/m<sup>2</sup>, and at least one follow-up office visit after initiation of sc semaglutide. A total of four follow-up visits after baseline visit were included in this study, to ensure for at least a 6-month follow-up period. Patients with a previous diagnosis of type 2 Diabetes Mellitus were excluded from participation in this study. The study protocol was approved by the reference Hospital Ethics Committee (University Hospital Son Espases).

A total of 372 patients were consecutively included in the study. All patients were prescribed sc semaglutide with an out-of-label indication for weight reduction, as part of a structured program for the management of overweight and/or obesity that included diet and exercise counselling. A number of patients had been previously or currently prescribed drugs with an approved indication for weight management (GLP-1 analogue liraglutide and lipase inhibitor orlistat) or a clinical indication for weight management yet out of label, as other GLP-1 analogues (dulaglutide, exenatide LAR), selective serotonin reuptake inhibitors (SSRI), and topiramate. Diet counselling included a structured quantitative dietary recommendation with an average 500 kcal/day reduction from calculated baseline metabolic rate. Standardized Harris-Benedict's equations corrected for Lang's daily activity coefficient were used to calculate baseline metabolic rate. In line with Spanish Health

Authorities policy, sc semaglutide prescription for overweight or obesity management is not reimbursed, and all patients paid for this out-of-pocket prescription accordingly.

Height, weight, and BMI were recorded as baseline variables at initial visit. Also, concomitant use of drugs with a potential to reduce weight including topiramate, orlistat, SSRIs and current or previous use of other GLP-1 analogues in the last 6 months previous to index date was also registered. At initial visit, sc semaglutide was started at a dose of 0.25 mg once weekly according to label instructions, but subsequent dose titration was left to physician's judgement based upon effectiveness and Gastrointestinal (GI) intolerance (namely, incidence of nausea, vomiting or abdominal pain). Patients in this unit are regularly followed-up with office visits every 4-12 weeks, and weight, current sc semaglutide dose, use of background medications for weight loss, incidence of adverse events and persistence on sc semaglutide were systematically recorded at each visit and included for analysis. Safety data included serious adverse events, incidence of GI intolerance and incidence of other adverse events.

Primary effectiveness outcome in this study was absolute and percentage weight loss from baseline after initiation of sc semaglutide until last follow-up visit. Secondary objectives included persistence on sc semaglutide and drug dose, evaluated at each follow-up visit, incidence of non-serious/serious adverse events and/or GI adverse events, proactively requested to patients, and change in background use of drugs for weight loss. Subgroup analysis evaluated influence of previous GLP-1 analogues therapy and background use of anti-obesity drugs in weight loss.

## Statistical Analysis

Primary and secondary outcomes analysis was performed for patients attending the last office visit. Subgroup analysis for previous use of GLP-1 analogues and use of anti-obesity medication included all patients with at least one follow-up office visit (last observation carried forward). All data are expressed as mean  $\pm$  Standard Deviation (SD) for continuous variables and as percentage for categorical variables. Normally distributed variables were compared using two-sided T-Student test and categorical variables were compared using Chi-square test. A p value <0.05 was assumed as statistically significant for all comparisons (Statplus statistical package 2016©, AnalystSoft, Walnut, CA).

## Results

Table 1 shows baseline characteristics of patients included in this study. A total of 367 patients completed a first follow-up visit. On average, patients had a mean age of 50.25 years and a wide majority of them were females (78.36%). Mean BMI was 32.39 $\pm$ 5.24 kg/m<sup>2</sup>, with a balanced distribution among patients with overweight (29.7%), class I obesity (37.32%) class II and III obesity (together, 32.42%). Up to 36.26% patients were on previous pharmacological treatment for obesity, mostly SSRI agents, topiramate and orlistat, and up to 24.25% of this population initiated sc semaglutide switching from a previous GLP-1 analogue therapy, either currently in use or in the previous 6 months. In most cases (89.88%) previous GLP-1 analogue

was liraglutide with an average daily dose of 1.48 mg. Median duration of previous aGLP-1 therapy was 5.34 months and mean ( $\pm$ SD) weight reduction achieved was 3.25  $\pm$ 5.32 Kg (Table 2). Up to 32.01% of patients

in this subgroup had achieved a  $\geq$ 5% weight loss with previous aGLP-1 therapy.

Table 1: Baseline characteristics of patients.

Number (n)	367
Age, years (mean $\pm$ SD <sup>1</sup> )	50.25 $\pm$ 13.28
Gender (% female)	78.36%
BMI <sup>‡</sup> (mean $\pm$ SD)	32.39 $\pm$ 5.24
Normal Weight (BMI <25 kg/m <sup>2</sup> ) n, (%)	10 (2.7%)
Overweight (BMI 25-29.9 kg/m <sup>2</sup> ) n, (%)	109 (29.70%)
Obesity class I (BMI 30-34.9 kg/m <sup>2</sup> ) n, (%)	127 (34.60%)
Obesity class II (BMI 35-39.9 kg/m <sup>2</sup> ) n, (%)	70 (19.07%)
Obesity class III (BMI $\geq$ 40 kg/m <sup>2</sup> ) n, (%)	49 (13.35%)
Use of AOM <sup>§</sup> at baseline (%)	36.26%
SSRI <sup>¶</sup>	21.98%
Topiramate	12.09%
Orlistat	10.99%
Previous use of aGLP-1 <sup>‡</sup> n, (%)	89 (24.25%)
Liraglutide n, (%)	80 (89.88%)
Exenatide o/w n, (%)	5 (5.62%)
Dulaglutide n, (%)	4 (4.49%)
Median duration of previous aGLP-1 therapy (months) (interquartile range)	5.34 (6.28-4.37)

SD: Standard Deviation

‡BMI: Body Mass Index

§AOM: Anti-obesity Medication

¶SSRI: Selective Serotonine Re-uptake Inhibitor

‡aGLP-1: Glucagon-like Peptide 1 against.

Table 2: Weight reduction throughout follow-up.

	1 <sup>st</sup> Office visit	2 <sup>nd</sup> Office visit	3 <sup>rd</sup> Office visit	4 <sup>th</sup> Office visit
Number of patients	367	354	338	288
Follow-up (months) (median; interquartile range)	2.0 (1.53-3.02)	4.83 (4.2-5.6)	7.06 (6.05-8.06)	10.70 (9.45-11.48)
Absolute Weight Loss (Kg) (mean $\pm$ SD <sup>1</sup> )	3.50 $\pm$ 2.51	5.72 $\pm$ 3.17	6.59 $\pm$ 3.24	7.97 $\pm$ 3.42
Percentage Weight Loss (%) (mean $\pm$ SD)	3.97 $\pm$ 2.64	6.49 $\pm$ 3.31	7.49 $\pm$ 4.47	9.13 $\pm$ 3.86
Patients with Weight Loss $\geq$ 5% (%)	28.81%	62.69%	77.03%	88.07%
Patients with Weight Loss $\geq$ 10% (%)	-	11.92%	16.25%	30.27%
Use of AOM <sup>§</sup> (%)	36.78%	36.26%	37.93%	28.81%*
Dose of semaglutide				
0.25 mg (%)	5.79%	6.22%	5.92%	5.35%
0.50 mg (%)	81.40%	77.78%	73.92%	71.19%
1.0 mg (%)	12.81%	16.00%	20.16%	23.46%
Persistence on semaglutide	94.82%	91.5%	88.86%	86.33%

SD: Standard Deviation

§AOM: Anti-obesity Medication

\*p<0.05 vs. baseline (Chi-square test)

## Weight Reduction

Table 3 and (Figures 1&2) show changes in BMI and body weight throughout consecutive office visits. After a median follow-up of 10.7 months up to 311 patients attending the last office visit,

achieved a weight loss of 7.97 $\pm$ 3.42 kg (9.13 $\pm$ 3.86% of baseline body weight), and weight loss was achieved gradually in a time-dependent fashion. By the end of study observation period, 88.07% and 30.27% of patients had achieved a  $\geq$ 5% and  $\geq$ 10% weight loss, respectively, as compared to baseline body weight.

**Table 3:** Weight reduction (LOCF)\* according to previous use of GLP-1 analogues

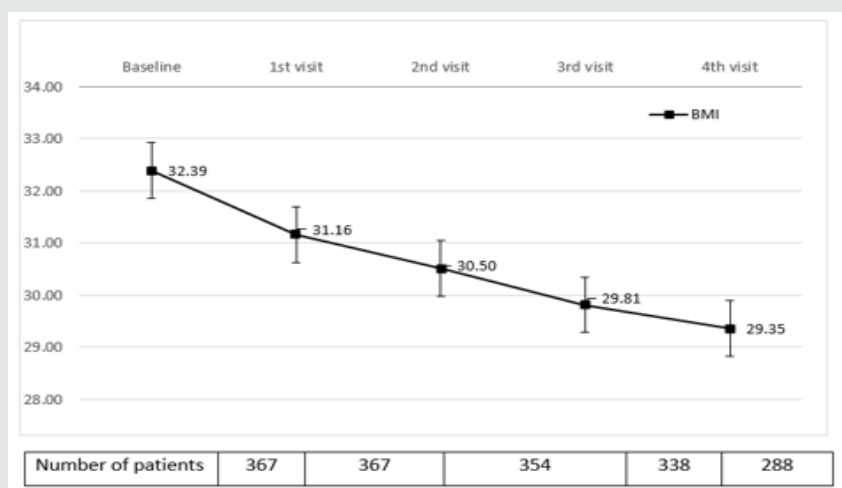
	Previous use of aGLP-1	No previous use of aGLP-1	p Value
Number (n)	89	278	
Follow-up (months) (median; interquartile range)	7.55 (6.3-8.7)	7.11 (6.15-8.05)	ns
Baseline BMI <sup>‡</sup> (kg/m <sup>2</sup> ) (mean ±SD <sup>1</sup> )	32.64 ±5.32	32.25 ±5.30	ns
Previous Weight Loss (kg) (mean ±SD)	3.25 ±5.32	NA	NA
Weight Loss (kg) (mean ±SD)	5.08 ±2.52	6.51 ±2.79	<0.001
%Weight Loss (%) (mean ±SD)	5.58 ±2.96	7.42 ±3.02	<0.001
Use of AOM <sup>§</sup> (%)	32.58%	37.05%	ns
Persistence on index drug (%)	86.9%	88.4%	ns

\*LOCF: Last observation carried forward

<sup>1</sup>SD: Standard Deviation

<sup>‡</sup>BMI: Body Mass Index

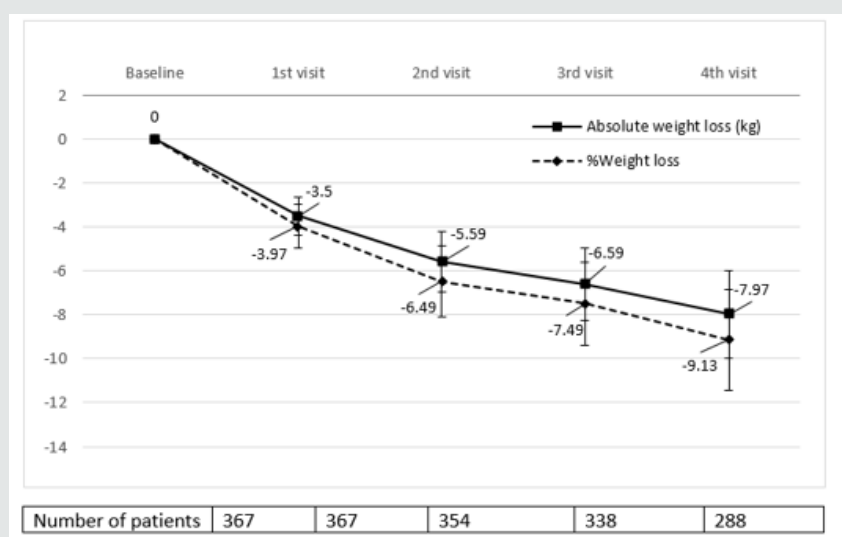
<sup>§</sup>AOM: Anti-obesity Medication



**Figure 1:** Evolution of BMI $\alpha$  after initiation of sc Semaglutide\*.

$\alpha$ BMI: Body mass index expressed in Kg/m<sup>2</sup>

\*Expressed as median values. Bars represent  $\pm$  standard deviation.



**Figure 2:** Absolute and Percentage weight loss after initiation of sc semaglutide\*.

\*Expressed as median values. Bars represent  $\pm$  standard deviation.

Tables 3 and 4 show changes in body weight according to previous use of GLP-1 analogue therapy and concomitant use of anti-obesity drugs, respectively. As stated before, up to 24.25% patients had switched to sc semaglutide from treatment with a GLP-1 analogue in the previous six months, mostly liraglutide. This subgroup of patients had achieved a previous weight reduction of  $3.25 \pm 5.32$  Kg after a median follow-up of 5.34 months (interquartile range, 4.12-6.57 months). Patients without previous use of a GLP-1 analogue, reduced significantly more weight than patients switching from a previous GLP-1 analogue to sc semaglutide, after

a similar follow-up period (last observation carried forward);  $6.51 \pm 2.79$  kg (7.42% of baseline body weight) vs.  $5.08 \pm 2.52$  kg (5.58%), respectively ( $p < 0.001$ ). No differences were found for concomitant use of other anti-obesity medications and persistence on sc semaglutide was quite similar between both groups (Table 3). Conversely, sub analysis of weight reduction according to concomitant use of any anti-obesity medication did not yield any significant differences between both subgroups, neither in baseline BMI, nor in the magnitude of weight loss (last observation carried forward), or in the persistence on sc semaglutide (Table 4).

**Table 4:** Weight reduction (LOCF)\* according to previous use of anti-obesity medication

	Use of AOM	No use of AOM	p Value
Number (n)	133	234	
Follow-up (months) (median; interquartile range)	7.09 (8.6-6.1)	7.62 (8.13-6.21)	ns
Baseline BMI <sup>‡</sup>	$32.23 \pm 5.32$	$32.75 \pm 5.56$	ns
Weight Loss (kg) (mean $\pm$ SD <sup>1</sup> )	$6.23 \pm 2.44$	$6.01 \pm 3.54$	ns
%Weight Loss (%) (mean $\pm$ SD)	$6.74 \pm 2.45$	$6.75 \pm 3.97$	ns
Persistence on index drug (%)	87.2%	88.1%	ns

\*LOCF: Last observation carried forward

<sup>1</sup>SD: Standard Deviation

<sup>‡</sup>BMI: Body Mass Index

**Table 5:** Safety and tolerability of sc semaglutide

	1 <sup>st</sup> Office visit	2 <sup>nd</sup> Office visit	3 <sup>rd</sup> Office visit	4 <sup>th</sup> Office visit
Number of patients	367	354	338	311
Patients with GI intolerance*, n (%)	66 (17.98%)	28 (7.9%)	12 (3.5%)	8 (2.5%)
Serious adverse events <sup>1</sup> , n (%)		2 (0.5%)		1 (0.3%)
Patients missed from Follow-up, n (%)	5 (1.3%)	13 (3.54%)	16 (4.51%)	27 (7.98%)

\*GI (Gastrointestinal) intolerance included nausea, vomiting, abdominal pain or diarrhoea.

<sup>1</sup>One patient admitted to hospital for urinary sepsis, one patient diagnosed of gross bowel cancer and one patient with myocardial infarction.

### Therapeutic Persistence, Drug Dose and Background Anti-Obesity Medication Use

A total of 311 patients did attend the fourth and last office visit included in this study (84.74%). Persistence on sc semaglutide was high throughout consecutive office visits, with up to 268 patients out of 311 (86.18%) attending the last office visit being persistent to the drug. Up to 61.19% of patients remained on an initially prescribed semaglutide dose of 0.5 mg (after initial up titration) throughout consecutive office visits and 33.46% of patients were on the 1.0 mg dose by the last office visit. Concomitant use of other anti-obesity drugs remained unchanged throughout follow-up visits, and only in the last office visit a statistically significant 7.45% reduction in use of other agents was detected, mostly affecting orlistat use.

### Safety and Tolerability

Regarding safety, few severe adverse events were reported throughout the follow-up period. A 66 year-old female was admitted to hospital due to urinary sepsis, a morbid obese 54 year-old male patient was diagnosed of gross bowel cancer requiring surgery and a 61 year-old patient suffered a non-lethal myocardial infarction.

Additionally, a patient accidentally administered 5 consecutive daily doses of 0.25 mg of sc semaglutide and reported on nausea and vomiting during two days, but her condition improved after stopping the medication, and after two weeks, the patient resumed correctly weekly administration of sc semaglutide. A total of 66 patients (17.98%) complained on GI symptoms at initial follow-up visit, and this percentage did reduce significantly in subsequent follow-up visits (Table 5). Most of these patients complained of nausea and abdominal pain, that in some cases deserved transient interruption of medication or use of omeprazole, and in 14 patients led to definitive interruption of medication. Other reasons for treatment abandonment included lack of effectiveness or inability to afford for treatment costs, as reported by up to 19 patients. A patient with a baseline BMI of 42.3 kg/m<sup>2</sup> was derived to bariatric surgery after 3 months of sc semaglutide 1.0 mg, with a weight loss of 5.3 kg from baseline.

### Discussion

In this observational study we evaluated weight reduction associated to out-of-label use of sc semaglutide in a patient population with overweight or obesity as part of a pragmatic

strategy for weight management including diet and physical activity counselling, and in selected cases prescription of drugs with a potential for weight loss. Patients included in this study represent an average profile of patients typically attending an obesity clinic in a private setting; middle aged patients with a high proportion of women and an average baseline BMI >30 kg/m<sup>2</sup>. Conversely, we found a lower percentage of patients with morbid obesity, as compared to Spanish public health system obesity units, where most patients are morbidly obese and referred to for consideration of bariatric surgery [20]. A substantial proportion of patients included in this study were previously on pharmacological therapy for weight loss. In Spain, according to the 2016 official position statement by the Spanish Society for the Study of Obesity (SEEDO) [21], only lipase inhibitor orlistat, combination of opioid receptor antagonist/antidepressant naltrexone/bupropion and GLP-1 agonist liraglutide are approved drugs for medium and long-term obesity management in patients with a BMI >30 kg/m<sup>2</sup> or >27 kg/m<sup>2</sup> with major comorbidities, when a structured program including diet and lifestyle changes fails to promote a weight loss >5% after 3 to 6 months of follow-up. Conversely, the 2016 clinical practice guidelines for medical care of patients with obesity issued by the American Association of Clinical Endocrinologists and the American College of Endocrinology (AAACE/ACE) [22] include lorcaserin, phentermine/topiramate ER (extended release) combination and SSRI therapy for selected patients as medications for chronic weight management.

Taking in mind the strong correlation between obesity and depressive mood disorder [23,24], it is not surprising that up to 21.98% of our patients were on SSRI (mostly fluoxetine) and in some cases with a coexisting indication for binge eating disorder or night eating syndrome. Eighty-nine patients in this study were using or had used in the past six months a GLP-1 analogue for weight reduction. Liraglutide was by far the most frequently used drug with an average daily dose of 1.48 mg which is lower than the approved dose of 3.0 mg od for weight reduction. Lack of reimbursement by Spanish public health system for liraglutide in obese subjects probably plays an important role in this low average dose used by patients, as treatment cost is directly dose-dependent. This issue has been acknowledged as a major limitation for treatment accessibility in our country, as stated by SEEDO guidelines [21]. Nevertheless, despite this low dose, patients on liraglutide achieved an average weight loss of 3.25 kg, accounting for >3% of baseline weight, after a median period of 5.34 months. Interestingly, the clinical development program for liraglutide LEAD (Liraglutide Effect and Action in Diabetes) included 4,456 patients with type 2 Diabetes with an average baseline BMI of 31.83 kg/m<sup>2</sup>, and age 55.87 years old. Weight loss associated to liraglutide 1.2 and 1.8 mg ranged 2.3 to 2.8 kg, respectively, after 26 to 52 weeks [25-30]. A similar baseline BMI in an older population was associated to a lower weight loss as compared to patients in our study. A possible explanation for this could be differences in age, as Mezquita et al., demonstrated in their liraglutide survey Diabetes Monitor [31]. In this real-world web-based survey, patients with type 2 Diabetes

under 50 years old lost significantly more weight as compared to patients over 60 years old. Nevertheless, potential differences in the response to GLP-1 analogues in a population without Diabetes cannot be excluded, as clear differences in GLP-1 biology in patients with type 2 Diabetes as compared to normal individuals have been detected [33], namely reduction of GLP-1 secretion in response to oral intake and reduction of insulinotropic potency of GLP-1 [34,35].

Patients in our study gradually achieved a clinically significant weight loss of 7.97 kg by the last office visit, accounting for 9.13% of initial body weight, after a median follow-up of 10.7 months. By the end of the study, 88.07% and 30.27% of patients attending the last office visit included in the observation period had achieved a ≥5% and ≥10% weight loss, respectively. According to SEEDO guidelines [21], a sustained weight loss of 3-5% of body weight is associated to clinically significant improvements in metabolic factors like blood glucose and plasma lipid concentrations, and reduces risk for development of Diabetes, with higher weight loss having the potential to reduce long-term cardiovascular complications. Conversely, AAACE/ACE guidelines for obesity management recommend a weight-loss goal of 5-10% (≥15% in some circumstances) to induce improvements of comorbidities associated to overweight or obesity [22].

Interestingly, most patients included in the study remained in the 0.5 mg od dose, and only 33.46% of patients increased to the 1.0 mg od dose at any office visit. Again, rather than GI intolerance or perceived effectiveness, we believe that economic constraints play a major role in the capability of patients to afford for higher doses of sc semaglutide. Throughout follow-up, use of other medications with a potential to reduce weight did not experience a substantial change except for last office visit, in which a 7.45% reduction was observed, affecting mostly to orlistat use. A reduction in meal size and fat content to avoid nausea, which is a common advice given to patients on GLP-1 analogues [17,36] could explain this observed reduction in orlistat use.

Persistence on sc semaglutide was high throughout study observation period, with more than 86.33% of patients using the drug by the last office visit after a median of 10.70 months. This persistence is comparable to that observed in a recent publication by our group [37] in patients with type 2 Diabetes in a real-world setting using sc semaglutide under approved indication for glucose management, with a full reimbursement by public health system. As opposed to patients in our study, with an out-of-pocket indication for weight loss, this high persistence is reflecting in our opinion, a high degree of patient's perceived effectiveness of sc semaglutide for weight reduction. Patients' satisfaction was not specifically measured in this study but indeed a perception of successful weight management was frequently referred by patients to treating physicians. Additionally, a low percentage of patients complained of GI intolerance, mostly nausea and abdominal pain, and in most cases, these symptoms were mild to moderate in intensity and transient, thus allowing for treatment continuation. Up to

19 patients attending office visits declared inability to afford for treatment cost, despite good tolerance and significant weight loss. Few serious adverse events were seen in this study, none of them with a potential direct relationship to the use of sc semaglutide. Furthermore, overall persistence on sc semaglutide in this study was higher than that reported for other GLP-1 analogues in patients with type 2 diabetes in other real-world setting studies [38,39].

In 2010, Astrup and colleagues published the results of a trial evaluating for the first time, efficacy and tolerability of liraglutide in adult obese patients without diabetes [16]. Patients randomized to 1.2 to 3.0 mg of liraglutide lost 4.8 to 7.2 kg compared with 2.8 kg with placebo after a 20-week follow-up period, setting the evidence for use of liraglutide in obesity. These results represent a deeper weight reduction in obese patients without diabetes, as compared to patients with type 2 diabetes in the LEAD program, and are closer to those observed in the subgroup of patients with a previous treatment with liraglutide in our observational study, despite differences in study design and observation period.

In 2018, O'Neil et al. published the results of a phase 2 trial evaluating efficacy and safety of daily sc semaglutide compared to liraglutide and placebo in 957 obese individuals with a baseline BMI of 39.3 kg/m<sup>2</sup> and age 47 years-old [18]. Patients randomized to 0.05 to 0.4 mg of sc semaglutide od lost -6.0% (0.05 mg), -8.6% (0.1 mg), -11.6% (0.2 mg), -11.2% (0.3 mg), and -13.8% (0.4 mg) as compared to -7.8% of initial body weight in patients randomized to liraglutide 3.0 mg od, throughout 52 weeks of treatment. In this study, proportion of patients with  $\geq 5\%$  and  $\geq 10\%$  weight loss vs baseline body weight ranged 54-90% and 19-72%, respectively, across different sc semaglutide doses. In our study, calculated average weekly sc semaglutide dose was 0.59 mg, which results in an estimated daily dose of 0.084 mg, close to the 0.1 mg od dose arm in the study by O'Neil et al., and with similar results in terms of weight loss (9.13% vs 8.6%) and proportion of patients with  $\geq 5\%$  and  $\geq 10\%$  weight loss (88% and 30% vs 67% and 37%, respectively). All sc semaglutide doses were generally well tolerated, with no new safety concerns. The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, as seen previously with GLP-1 agonists in patients with type 2 Diabetes and rarely led to discontinuation of treatment. No patient complained on symptoms suggesting hypoglycaemic episodes, reassuring the safe use of the drug in a population with normal glucose metabolism. A comprehensive clinical development program, the Semaglutide Treatment Effect in People with Obesity (STEP) program is now undergoing, aiming to investigate the effect of sc semaglutide on weight loss, safety, and tolerability in adults with obesity or overweight. The program comprises 5 randomized clinical trials for which results will be available through 2020-2021[19]. For all trials, the primary end point is change from baseline to end of treatment in body weight. Participants have a mean age of 46.2 to 55.3 years, are mostly female (mean 74.1%-81.0%), and have a mean BMI of 35.7 to 38.5 kg/m<sup>2</sup>.

Our study represents the first published evidence for effectiveness and safety of sc semaglutide with a weekly administration in the management of overweight and obesity in adults without diabetes in a real-world setting. An important point in this study, derived from its observational nature in real practice conditions, is that patients paid for sc semaglutide treatment and still a high percentage of them remained persistent to the therapy. Treatment adherence is one of the major drivers for the gap between efficacy observed in clinical trials and effectiveness found in real practice in chronic conditions like type 2 Diabetes [40], and obesity shares similarities with it, both in their chronic nature and in their pathophysiology. Weight reduction is a strong signal for patients' perception of effectiveness that reinforces treatment adherence and this is probably one of the reasons for the high treatment adherence found in our study. Undoubtedly, treatment cost and treatment adherence will significantly impact effectiveness of anti-obesity drugs in future real-world studies.

Our study has several limitations derived from its real-world descriptive nature. First, the lack of a control group does not allow to assign achieved weight loss to the solely effect of sc semaglutide, although previous evidence from randomized trials shows a similar degree of weight loss associated to the drug. Second, a number of patients were missed from follow-up for weight evolution, so again a selection bias overestimating treatment effect cannot be excluded, being this is a typical limitation of real-world studies. Third, a number of patients were included in this study with current use of other drugs with a potential for weight loss, both oral medications and GLP-1 analogues, so a potential confounding effect of these treatments cannot be completely excluded. Nevertheless, we performed a subgroup analysis where oral anti-obesity medications were not found to impact significantly on weight reduction and conversely, previous use of GLP-1 analogues was associated to a significantly lower weight loss, assuming that part of the potential for weight reduction associated to GLP-1 agonist therapy had already been achieved in those patients. Finally, it is not usual that an observational study reporting on effectiveness and safety of a drug in real practice conditions is published before gaining regulatory approval for the specific indication, as efficacy and mostly safety are important issues that must be first addressed by randomized clinical trials, and the authors deeply acknowledge this fact. Nevertheless, several important questions must be kept in mind in this regard; first, sc semaglutide has been approved by regulatory agencies in most developed countries for use in patients with type 2 diabetes and conditions for reimbursement in Spain include coexisting obesity, which virtually affects most patients with type 2 Diabetes. Second, liraglutide, a GLP-1 analogue with a similar molecular design and pharmacological properties has been approved for weight reduction in patients with obesity and third, given the shortage of effective treatments to treat obesity and the barriers that treatment cost may represent for patients' accessibility to such therapies, the authors believe that evidence provided by this study is timely, and of scientific interest.

## Conclusion

In conclusion, in this observational study in real practice conditions, we have demonstrated that sc semaglutide at a weekly dose of 0.5 to 1.0 mg administered to patients with overweight or obesity in the pragmatic context of a structured program along with diet and lifestyle recommendations resulted in a sustained, safe and affordable clinically significant weight reduction. Given the limitations of a retrospective observational study, we will need to confirm these results with the forthcoming results of the STEP program and contrast them with results from other groups in a real practice setting which for sure will be coming up in future. Until then, we consider that weekly sc semaglutide represents a useful tool for helping patients in their long-term struggle, along with diet and lifestyle changes, to increase their chances to arrive to and maintain a healthy body weight.

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