

¿Promueve la semaglutida la adherencia a las medidas de estilo de vida para la pérdida de peso? Influencia en vida real de la semaglutida en las personas que viven con sobrepeso/obesidad en la pérdida de peso y el ejercicio físico

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Could semaglutide promote lifestyle interventions? Influence of semaglutide among people living with overweight/obesity on weight loss and physical activity in a real-world scenario

Abstract

Lifestyle interventions are the cornerstone of weight management, especially physical activity. Semaglutide is an effective and safety therapy for weight loss and could enhance the adherence to lifestyle interventions. Thus, the combination of semaglutide and physical activity could improve medical, functional, and psychological health.

69 PWO who previously failed to achieve or maintain a significant weight loss despite lifestyle interventions were evaluated baseline and after 3 months. All patients were prescribed weekly sc semaglutide with an out-of-label indication for weight reduction. Body composition was evaluated using a bioimpedance device. Physical activity was auto reported.

69 PWO (82.6% ♀, 43.7±1years, and 34.3±6kg/m²) after 3 months of semaglutide there was a significant reduction in weight (96.1±20.9 vs 91.3±19.7kg; p<0.01) and fat mass (41.6±15.4 vs 30.4±7.5kg; p<0.0001). No differences were seen regarding free fat mass (32.1±8.4 vs 30.4±7.5kg; p=0.2). Moreover, the proportion of PWO with regular exercise was increased (15.9 vs 52.2%; p<0.001). Logistic regression analysis showed that the increase in daily exercise predicted a greater weight loss (p=0.003).

For the first time we identify that the treatment with low dose semaglutide may help promoting the adoption of healthy lifestyle habits and, thus, resulting in positive outcomes beyond body weight.

Key words: physical activity; lifestyle interventions; semaglutide; weight loss; obesity; anti-obesity drugs

Highlights

- Semaglutide is an effective weight management treatment in PwO in a real-world scenario at short term without a negative impact on fat-free mass in persons who previously failed to achieve or maintain significant weight loss with lifestyle interventions only.
- Low dose semaglutide could improve the adherence to a regular physical activity routine.
- The promotion of healthy lifestyle attitudes as physical activity has a beneficial effect on physical and mental health beyond weight loss/maintenance.

¿Promueve la semaglutida la adherencia a las medidas de estilo de vida para la pérdida de peso? Influencia en vida real de la semaglutida en las personas que viven con sobrepeso/obesidad en la pérdida de peso y el ejercicio físico.

Resumen

La semaglutida es un tratamiento efectivo y seguro para la pérdida de peso y aumentaría la adherencia a las intervenciones de estilo de vida. La combinación de semaglutida y el ejercicio físico podría mejorar salud, funcionalidad y salud mental de las PWO.

69 PWO que previamente no han conseguido una pérdida de peso significativa fueron evaluados al inicio y a los 3 meses. Todos los pacientes recibieron semaglutida subcutánea semanal con indicación *out-of-label* para pérdida de peso. La composición corporal se midió mediante bioimpedancia. La actividad física fue autoreportada.

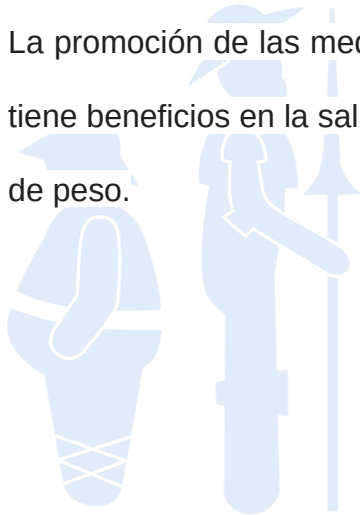
69 PWO (82.6% ♀, 43.7±años y 34.3±6kg/m²) después de 3 meses de semaglutida experimentan una reducción del peso (96.1±20.9 vs 91.3±19.7kg; p<0.01) y de la masa grasa (41.6±15.4 vs 30.4±7.5kg; p<0.0001). Sin diferencias significativas en la masa libre de grasa (p=0.2). La proporción de PWO que realiza ejercicio físico de forma regular incrementó (15.9 vs 52.2%; p<0.001) siendo el incremento en la realización de ejercicio físico el mejor predictor de la pérdida de peso (p=0.003).

Nuestro estudio sería el primero en mostrar que la semaglutida puede promover la adherencia a hábitos saludables, especialmente el ejercicio físico, resultando en beneficios para la salud más allá de la pérdida de peso.

Palabras clave: ejercicio físico; estilo de vida; semaglutida; pérdidas de peso; obesidad; medicamentos contra la obesidad

Puntos clave

- La semaglutida es un tratamiento efectivo para la pérdida/mantenimiento de peso en PWO en vida real y a corto plazo sin impacto negativo en la masa libre de grasa en personas que previamente no habían conseguido mantener/perder el peso deseado solamente con medidas de estilo de vida.
- Dosis bajas de semaglutida mejorarían la adherencia al ejercicio físico regular.
- La promoción de las medidas de estilo de vida, especialmente el ejercicio físico, tiene beneficios en la salud física y mental, más allá de la pérdida/mantenimiento de peso.



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Introduction

The prevalence of obesity has been rising in recent years reaching a pandemic status[1]. According to the new regional Obesity Report from the World Health Organization, not a single country in Europe is on track to stop the rise in obesity by 2025[1]. In Spain, in 2019 one in three persons between 3 and 24 years live with overweight or obesity[2]. In addition, lockdowns introduced to slow the spread of the SARS-CoV2 pandemic have increased the likelihood of weight gain[3]. It must be borne in mind that for every 5-unit increase in body mass index (BMI) above 25 kg/m², overall mortality increases by 29%, vascular mortality by 41%, and diabetes-related mortality by 210%[4]. People with a body mass index of 30-34,9kg/m² have a hazard ratio for overall mortality 40% higher than people with a normal bodyweight [5]. People with a BMI >40 kg/m² the increased hazard ratio approaches 100%[5]. Zhou et al. 2021 in a prospective cohort study of 381363 UK Biobank participants with a median follow-up of 11,2 years found that participants classified as metabolically healthy obesity compared to metabolically healthy non-obese patients had a significantly higher rates of developing diabetes, incident and fatal atherosclerotic cardiovascular disease, heart failure and respiratory diseases[6]. 13 cancer types can be attributed to excess body fat and also, obesity is associated with a poorer prognosis for various malignant conditions[7]. So, obesity must be treated at any age as a chronic, progressive and relapsing condition with multiple and serious comorbidities associated.

A sedentary behavior is adopted by an increasing number of persons. In Spain, in 2020, up to 6,4% of people older than 15 years considered themselves as sedentary[8]. The cornerstone of the management of PwO is lifestyle intervention. Lifestyle modifications are crucial to achieve the desired results. Choosing nutritionally dense foods and reducing the portion size to induce a negative calorie balance are mandatory in nutritional intervention. The improvement of sleep habits could help increasing satiety and fullness as well as activity levels during the day, promoting the preservation of lean body mass and reducing stress and anxiety[9]. Physical activity is highly effective in reducing cardiovascular mortality risk, independently of weight loss, especially when moderate to high intensity activities are involved. Gaesser et al. 2021 propose a weight-neutral strategy for obesity treatment, because weight loss is not consistently associated with lower mortality risk, whereas increased physical activity and exercise have been demonstrated to reduce mortality risk[10].

An objective of a 5-10% of weight loss is considered clinically important because it reduces cardiovascular risk factors and improves some comorbidities in PwO[11]. Nevertheless, aiming for larger weight losses, equal or more than 10%, could be necessary in those with BMI equal or greater than 35kg/m² or at high risk of developing obesity-related complications[11]. Participants in the Action for Health in Diabetes (Look AHEAD) trial were randomly assigned to either intensive lifestyle intervention or diabetes support and education. The first group lost less than 10% bodyweight after 1 year[12]. Therefore, lifestyle interventions could not be enough to reduce complications and, thus pharmacological treatment should be considered.

Adherence to lifestyle interventions to reduce weight or improve health is challenging[13]. Also, weight regain is a major concern. Anderson et al. 2001 in a meta-analysis of 29 long-term (4- or 5-years follow-up) weight loss studies, more than half of the lost weight was regained within two years, and more than 80% of weight lost was regained after five years since the intervention[14]. Furthermore, every attempt to lose weight is a challenge because weight fluctuations during weight loss attempts can be a factor for increased cardiovascular and mortality risk in people with type 2 diabetes (T2DM)[15].

In Spain, the use of pharmacological therapies to treat obesity is considered in patients with a BMI ≥ 30 kg/m² when a weight loss greater than 5% has not been achieved after 3-6 months of the initiation of a lifestyle program[16]. Also, patients with a BMI ≥ 27 kg/m² and obesity-related comorbidities the pharmacological treatment should be considered[16]. Daily subcutaneous liraglutide 3mg is nowadays the only GLP-1 analogue (aGLP-1) approved in the Spanish guidelines. The SCALE trial[17], with 3mg daily liraglutide among PwO for 56 weeks, 63.2% of patients (vs. 27.1% in the placebo group) lost 5% of their bodyweight, being this weight loss clinically significant and enough to reduce obesity related complications. Only 33.1% of patients (vs. 10.6% in the placebo group) lost more than 10% of their body weight. However, almost two thirds of the patients did not achieve the desired weight loss with the combination of liraglutide 3mg daily plus intensive interventional lifestyle modification.

Besides, aGLP-1 are the most effective pharmacological tool for weight reduction. The Semaglutide Treatment Effect in people with obesity (STEP trials 1-5) have included more than 5,000 participants and proved the efficacy and safety of semaglutide to reduce weight among PwO, with or without diabetes, in a dose-dependent manner[18]. Moreover, semaglutide has proved their superiority in terms of efficacy in comparison with liraglutide in the STEP 8 trial[19]. Actually, a reduction of 15.8% of weight with semaglutide 2,4 mg weekly vs a reduction of 6.4% with liraglutide 3mg daily was reported. Thus, participants who received semaglutide had significantly greater odds of achieving more than 10% weight loss with semaglutide compared to liraglutide[19].

The US Food and Drug Administration (FDA) and the National Institute for Health and Care Excellence (NICE) approved semaglutide 2.4 mg for use in chronic weight management among adults with obesity or overweight who have at least one metabolic weight-related condition, in combination with lifestyle intervention[20]. Despite the effectiveness and safety of semaglutide in reducing weight and improving cardiovascular health, the use of semaglutide to treat PwO without diabetes has not been approved in some countries like Spain, leading to its off-label use by healthcare providers. The aim of our work is to investigate whether weekly semaglutide decreases body weight and increases the adherence to lifestyle interventions, especially physical activity, in PwO in a real-world scenario.

Materials and methods

1. Subjects

This observational prospective study included 69 patients attending two obesity clinics from June to September 2021. These patients failed to achieve or maintain a significant weight loss despite lifestyle interventions, such as a tailored hypocaloric diet and a minimum of 150 minutes of exercise per week. Also, most of these patients were prescribed liraglutide 3mg previously, but it was stopped for different reasons, being the main one's lack of efficacy and its cost. After a throughout shared decision process involving the patient, in which understandable information regarding potential benefits and harms of subcutaneous semaglutide use were reviewed, a total of 69 patients with obesity (PWO) were included in the study. All patients were prescribed weekly sc semaglutide with an out-off-label indication for weight reduction among patients without concomitant type 2 diabetes. This treatment was an adjunctive therapy of a lifestyle intervention program and regular follow-up office visits. Eligibility criteria were as follows: (1) Patients older than 18 years with a BMI equal or greater than 27kg/m² with comorbidities related to obesity or a BMI equal or greater than 30kg/m². (2) Patients without a personal history of medular thyroid carcinoma, acute or chronic pancreatitis. (3) Patients who were able to understand the given information and capable to maintain a regular follow-up. (4) Patients who did consent to participate in the study. This study was conducted according to the World Medical Association Declaration of Helsinki. The study was approved by the Ethics Committee of the hospital. Informed consent was obtained from all subjects prior to study participation.

2. Interventions

Diet counselling included a tailored and structured quantitative diet with an average of 500kcal/day reduction from calculated baseline metabolic rate adjusted by physical activity. Besides, a minimum of 150 minutes of aerobic exercise per week was also prescribed. Regarding semaglutide titration, patients started with a dose of 0.25mg per week for the first two weeks and, depending on the tolerance and side effects, mostly gastrointestinal, this dose was titrated up to 0.5mg after two weeks of treatment. This dose was increased to 1mg once weekly after a minimum of four weeks of treatment when there was no significant improvement in anthropometric parameters. Patients were evaluated baseline, and after one and three months since the beginning with semaglutide.

3. Body weight

Height and weight were measured while each participant was wearing indoor clothing without shoes. Body mass index (BMI) was calculated as weight divided by height squared. Body composition was assessed with a bioimpedance device (InBody 270). Significant weight loss was defined as a reduction of more than 5% of the baseline weight. See figure 1.

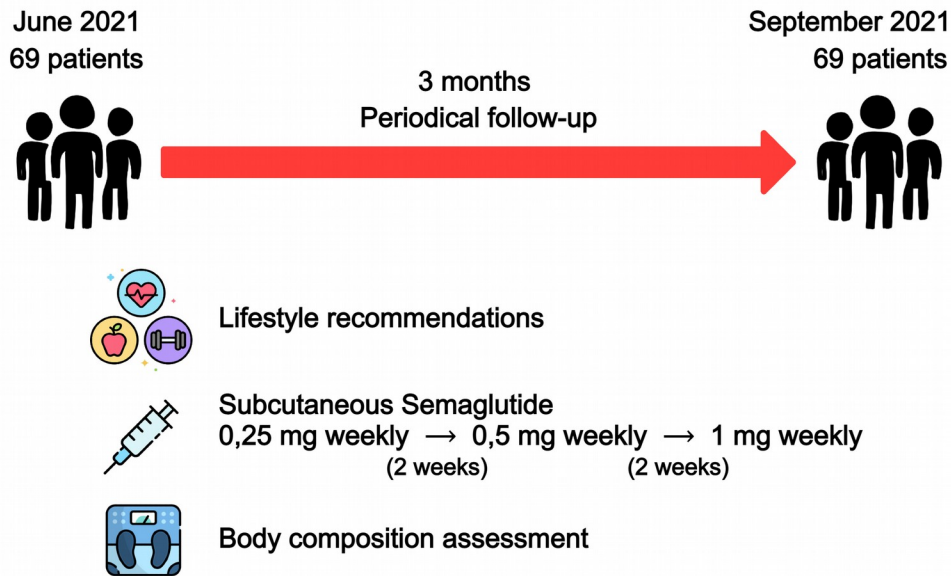


Figure 1: Study design.

4. Statistical Analysis

Statistical analyses were performed using the IBM® SPSS® Statistics Version 21.0. Initial analyses were descriptive and included calculation of mean, median and standard deviation for continuous variables and frequencies for categorical variables. The distribution of the sample was analyzed by the Kolmogorov-Smirnoff test. The three groups were compared regarding sociodemographic variables, BMI and BDI by using χ^2 tests for categorical variables and t tests and univariate analysis of variance (ANOVA) for continuous variables. The statistical significance level for all tests was set at an α of $p < 0.05$.

5. Study outcomes

Main outcome in this study was body weight loss after three months of treatment with semaglutide and its impact on lifestyle habits. A secondary outcome explored potential

independent predictors of weight loss among baseline characteristics, including physical activity, obesity age of onset, and the presence of psychological comorbidities. Weight loss and BMI reduction were compared using ANOVA for repeated measurements. Changes in prevalence of abnormal eating patterns were compared using X2 test for proportions. Potential independent predictors of weight loss (dependent variable) were evaluated using univariate and multivariate logistic regression analysis of the variance, with baseline characteristics as independent variables. For all statistical comparisons, a two-sided $p < 0.05$ was assumed for significance.

Results

1. Participants' baseline characteristics

PwO included in the study had a mean age of 43.7 ± 10.1 years and 82.6% (57/69) were women. Baseline weight and BMI were 96.1 ± 20.9 kg and 34.3 ± 6 kg/m², respectively. 46 out of 69 (66.7%) had an active job and only 10.1% (7/69) lived alone. When interviewing the patients, obesity started during childhood in 18 out of 69 (26.1%) and there was a familiar history of obesity in 40.6% (28/69).

Regarding comorbidities related to obesity, the most prevalent one among our patients was hypertension (17.4%), whereas dyslipidemia (5.8%), obstructive sleep apnea (1.4%) and orthopedic problems (4.3%) were less frequent. However, regarding psychological conditions, up to 17.4% of patients had a personal history of depressive disorder and only 4.3% had been diagnosed with a binge eating disorder. When

considering lifestyle habits, only 11 out of 69 patients (15.9%) reported more than 150 minutes of exercise per week.

2. Body composition and physical activity

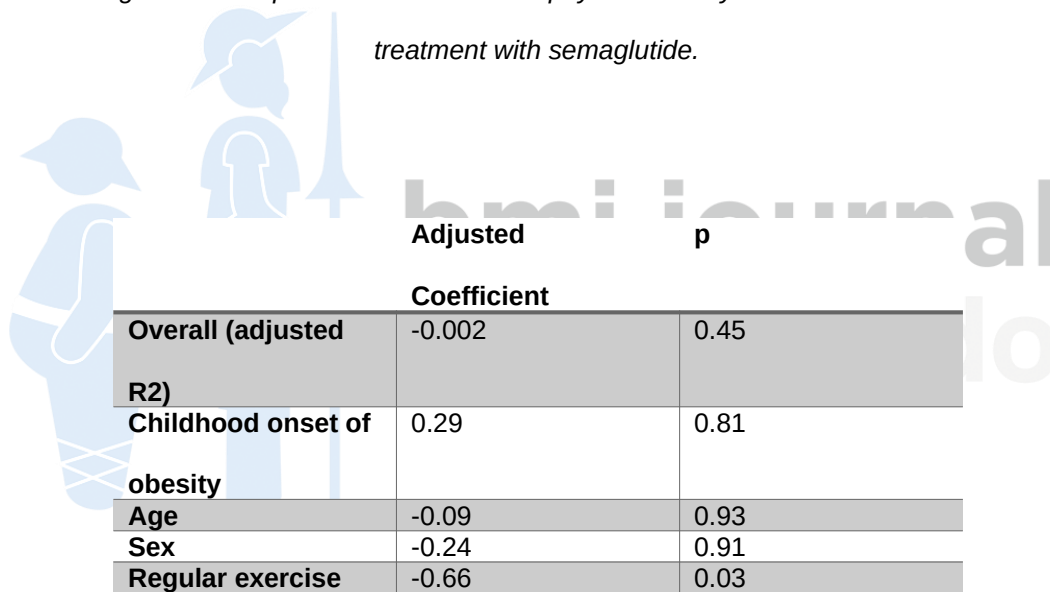
After three months of semaglutide, there was a significant weight and BMI reduction (96.1 ± 20.9 vs 91.3 ± 19.7 kg and 34.3 ± 6 vs 32.5 ± 5.6 kg/m²; $p < 0.0001$). In addition, PwO on semaglutide had a significantly fat mass reduction from baseline (41.6 ± 15.4 vs 30.4 ± 7.5 kg; $p < 0.0001$). However, no differences regarding free fat mass were seen after three months of treatment (32.1 ± 8.4 vs 30.4 ± 7.5 kg; $p = 0.2$).

Furthermore, when considering lifestyle habits, the proportion of patients that increased their exercise frequency up to 150 minutes per week was significantly higher after three months of treatment with semaglutide compared to baseline (15.9% vs 39.1%; $p < 0.0001$). Logistic regression analysis showed that the increase in daily exercise predicted a greater weight loss ($p = 0.003$). All these results are shown in table 1, table 2, figure 2 and figure 3.

	Baseline (N=69)	3 months of treatment with semaglutide	p
Weight (kg)	96.1±20.9	91.3±19.7	<0.0001
BMI (kg/m²)	34.3±6	32.5±5.6	<0.0001
FM (kg)	41.6±15.4	30.4±7.5kg	<0.0001
FFM (kg)	32.1±8.4	30.4±7.5kg	0.02
Regular exercise (%)	11 (15.9)	27 (39.1)	<0.0001

Data are expressed in mean±SD or absolute numbers and %. BMI: body mass index. FM: Fat mass. FFM: Fat-free mass.

Table 1. Changes in anthropometric variables and physical activity adherence after three months of treatment with semaglutide.



	Adjusted Coefficient	p
Overall (adjusted R²)	-0.002	0.45
Childhood onset of obesity	0.29	0.81
Age	-0.09	0.93
Sex	-0.24	0.91
Regular exercise	-0.66	0.03

Table 2. Multivariate Logistic Regression Analysis of Factors Associated to Weight Loss as Dependent Variable.

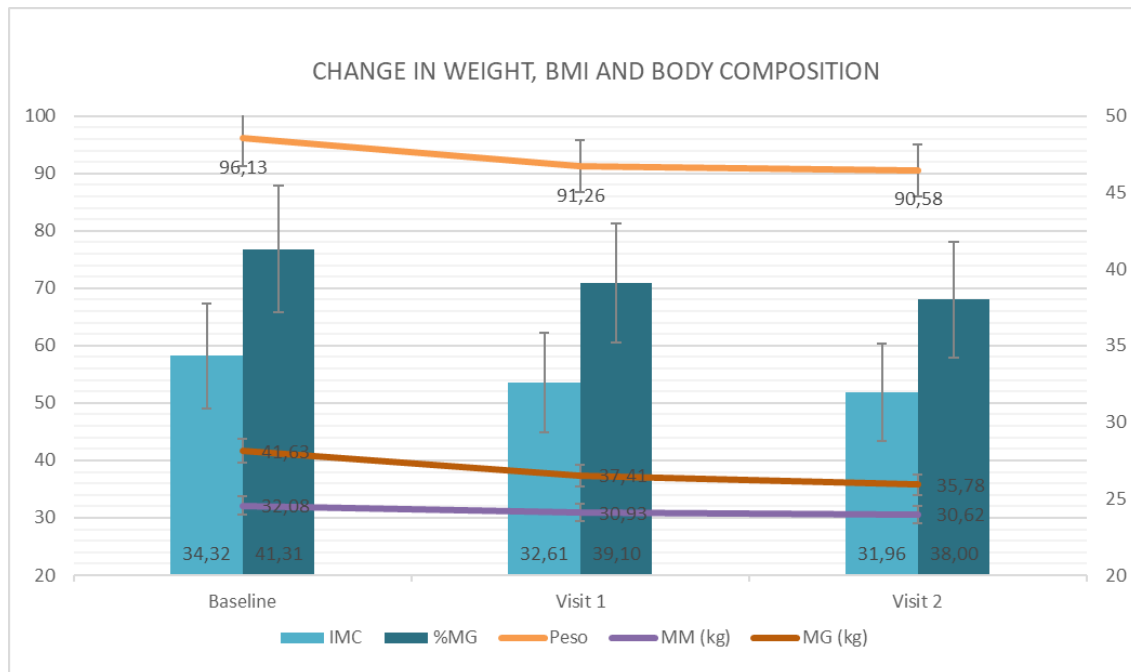


Figure 2. Changes in anthropometric variables after three months of treatment with semaglutide. Data are expressed in mean±SD or absolute numbers and %. BMI: body mass index. FM: Fat mass. FFM: Fat-free mass.

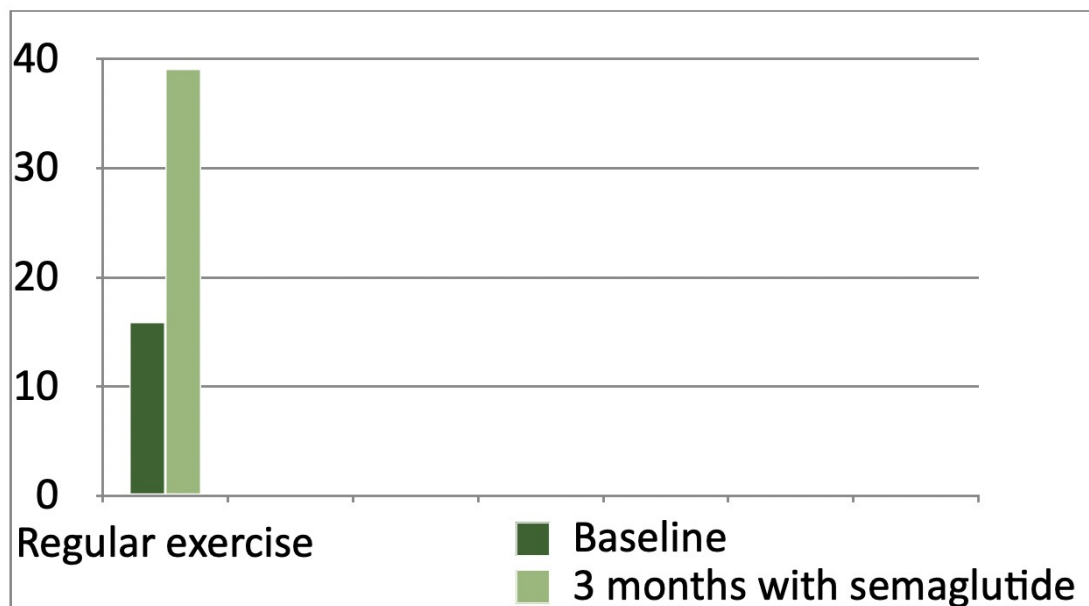


Figure 3. Changes in regular exercise frequency after three months of treatment with semaglutide.

Discussion

We found that the use of semaglutide achieves a significant reduction in weight, BMI and fat mass without a negative impact in fat-free mass[21]. Previous studies have shown absolute weight loss up to 4.6 kg and 6.5 kg associated with the use semaglutide at doses of 0.5 mg and 1.0 mg respectively over 40 weeks. In addition, comparative trials have shown that semaglutide 1.0 mg produces greater weight loss than dulaglutide 1.5 mg (6.5 kg vs. 3.0 kg)[21] and that subcutaneous semaglutide at a dose greater than 0.2 mg per day is associated with a greater body weight reduction than liraglutide 3.0 mg daily[21]. However, different results were reported by Alsugair et al. 2021 which found that weekly semaglutide at doses of 0.5mg and 1 mg produced a greater weight reduction than liraglutide at 0.6 mg daily (2.42 and 3.06 kg, respectively), although this difference was not seen when liraglutide 1.2 and 1.8 mg was used[22].

Our study is the first to show that aGLP-1 treatment with 0.5-1mg of weekly semaglutide could increase the adoption of healthy lifestyle habits and promote a greater adherence to exercise recommendations provided by the health care provider. Besides its effects on weight reduction, increases in cardiorespiratory fitness and physical activity are consistently associated with greater reductions in mortality risk than intentional weight loss[10]. In a meta-analysis, Saeidifard et al. 2019, showed that, when compared with no exercise at all, resistance training alone was associated with 21% lower all-cause mortality, and increased up to 40% when combined with aerobic exercise[23]. The promotion of physical activity and exercise programs that combine aerobic and resistance training must be a priority in health promotion interventions. Pharmacological

treatments such as semaglutide, could help PwO to maintain an adequate adherence to such programs and, thereby, increasing their effectiveness.

However, it is also important to diminish adiposity to reduce obesity complications. In this regard, lifestyle intervention will not always be enough to reduce a significant body weight. Lifestyle interventions show up to 5 to 8% from initial weight loss after 4-6 months of intensive and supervised treatment[20]. Moreover, additional weight loss is recommended to reduce obesity-related complications. 10 to 15% weight loss has shown significant improvements in HbA1c, blood pressure and lipids. In fact, a reduction of more than 10% weight loss is required to reduce sleep apnea, nonalcoholic steatohepatitis and preventing cardiovascular major events[24]. For this reason, some authors highly recommend a goal of 10 to 20% weight loss[25]. When reduction in body fat is the objective, we should aim to produce effective results at the first attempt because weight variability is an extremely high-risk factor. Patients with the highest weight variability have a 59% higher risk of any coronary event, an 82% higher risk of a major coronary event or death, a 75% higher risk of any cardiovascular event, a 99% higher risk of myocardial infarction, and a 92% higher risk of stroke[15].

However, between 35-50% of patients undergoing lifestyle interventions not only fail to lose any significant amounts of weight but, even more importantly, they fail to maintain it at long term[13]. These data could be wrongly interpreted as lifestyle intervention strategies showing limited efficacy in the improvement of body composition. In fact, strategies combining exercise and aGLP-1 therapy improve healthy weight loss

maintenance more than pharmacological treatment does alone[26]. In this trial, only the combination of lifestyle intervention through exercise and aGLP-1 was associated with improvements in HbA1c, insulin sensitivity, and cardiorespiratory fitness[26]. Stinson et al. 2020 compared the adherence to a dietary protocol with and without calorie restriction in lean healthy patients and in PwO, with the food being provided. Results indicated that there were no differences regarding dietary adherence between lean individuals and PwO and the adherence was not associated with hunger or adiposity[27]. The authors suggested that non-adherence or lack of willpower are exclusive among PwO is false and this belief may perpetuate weight bias and stigma[27]. In a secondary analysis of the DiOGenes study, they found that higher self-imposed levels of physical activity may improve the cardiometabolic risk profile during weight loss and help maintain weight loss in the long term[28]. Moreover, in a systematic review and meta-analysis they found that the increase in physical activity is the most consistent positive correlate of weight loss maintenance[29]. Even, the *FTO* gene, which is the one that harbors the strongest known susceptibility for obesity is attenuated by 27% in physically active adults, highlighting the importance of physical activity particularly in those PwO genetically predisposed to obesity[30].

In the STEP 1 trial, they found a better performance in physical test and an increase in health-related quality of life among PwO treated with 2.4mg of weekly semaglutide[18]. In fact, participants were more likely to have a clinical improvement of physical functioning. However, despite our study used lower doses of semaglutide than in the STEP trials, we also reported a significant increase in the adherence to physical activity

recommendations. Therefore, treatment with semaglutide could be a tool to increase the adherence to an irreplaceable intervention: nutrition, diet, sleep, and psychological management (Figure 4).

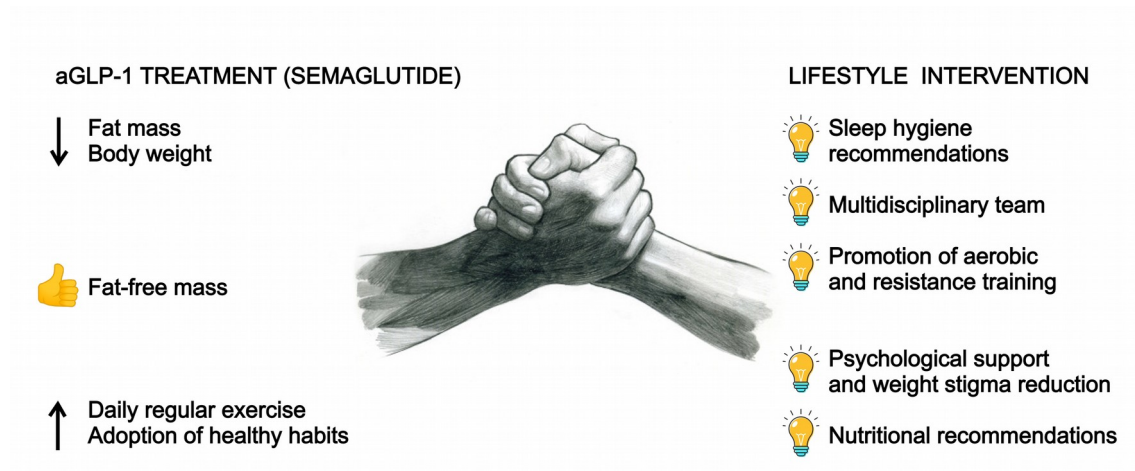


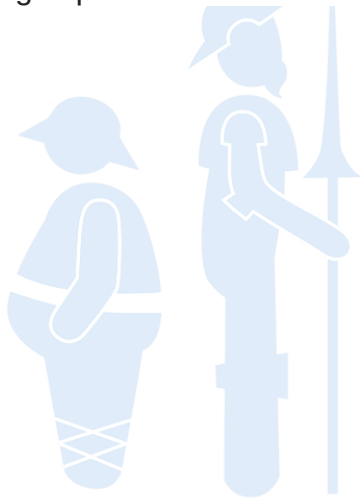
Figure 4. Semaglutide improves bodycomposition and promote lifestyle interventions

Our work has several limitations. First, it has a limited number of patients. As mentioned before, anti-obesity drugs are not reimbursed by the Spanish government. Therefore, people attending an obesity clinic and affording the use of semaglutide may have a higher socioeconomic status that could biased the results. In addition, physical activity was auto reported by the patients and not measured by any 24-hour activity recorder device, such as a smartphone with accelerometer, a smartwatch, among others. Also, the duration of the study can be seen as a strength or a limitation. We achieved significantly positive results in a short time, however it would be interesting to see the follow up of these patients in a long-term scenario, when weight loss tends to reach a

plateau. However, the data obtained in this work must be considered real-world data, which confirm and adds information to randomized control trials.

Conclusions

Semaglutide is an effective weight-loss treatment in PwO in a real-world scenario in the short term and without a negative impact on fat-free mass. Our study has been the first to identify that treatment with semaglutide, at doses 0.5-1mg weekly, may help promoting the adoption of healthy lifestyle habits and, in particular physical activity, resulting in positive outcomes beyond body weight.



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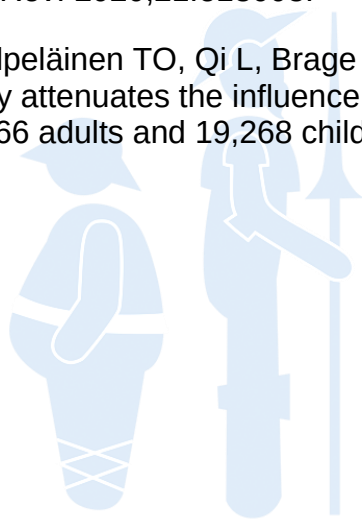
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