TITLE

ASSESSMENT OF BODY COMPOSITION AND PREVALENCE OF SARCOPENIA FOLLOWING INTENTIONAL WEIGHT LOSS WITH MEDICATIONS (SEMAGLUTIDE OR TIRZEPATIDE) IN INDIVIDUALS WITH OBESITY

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PROTOCOL

1.- BACKGROUND:

Medical treatment for obesity includes lifestyle modifications and pharmacological interventions designed to facilitate adherence to therapeutic regimens and support long-term weight maintenance. While a weight loss of 5–10% of initial body weight is known to help improve the symptoms of many obesity-related comorbidities, a sustained weight loss of ≥15% is required to achieve remission of complications or a reduction in mortality. This degree of weight loss can be attained through bariatric surgery or the use of second-generation anti-obesity medications—specifically GLP-1 receptor agonists, as well as dual and triple agonists [1,2]. Examples include semaglutide (2.4 mg) [3,4] and tirzepatide [5], both of which have been approved by the FDA and EMA and are available on the Spanish market as of 2024.

A primary limitation of pharmacological treatments remains the lack of reimbursement by public healthcare systems, which constrains the feasibility of long-term therapy [6]. Nevertheless, demand for such pharmacological treatments is growing, driven by their efficacy and safety profiles, characterized by limited and manageable side effects [7].

Clinical trials have primarily focused on outcomes such as the effectiveness of weight loss, improvements in cardiometabolic markers, adverse effects, and quality of life. However, there is an increasing awareness that significant weight loss is accompanied by a substantial reduction in lean body mass (fat-free mass), which can compromise an individual's health—posing risks such as sarcopenia and premature metabolic adaptation [8]. Consequently, new clinical studies are currently underway to investigate molecules that may help preserve skeletal muscle mass [9]. It is well established that weight loss achieved through highly restrictive diets or bariatric surgery leads to a loss of lean body mass—accounting for 20–35% of the total weight lost [10, 11], or an estimated 1.0–1.5 kg of lean mass for every 10 kg of weight lost (10–15%) [12]. Despite numerous pivotal studies on semaglutide (2.4 mg) and tirzepatide, data regarding changes in body composition remain very limited; such information is only available in the supplementary materials of the STEP-1 [13] and SURMOUNT-1 [14] clinical trials, which involved a limited number of patients. With semaglutide (2.4 mg), the 16.8 kg lost after 68 weeks of treatment consisted of 10.4 kg of fat mass and 6.9 kg of lean mass [13]. With tirzepatide (pooled doses ranging from 5–15 mg), participants lost 33.9% of their fat mass (-16.7 kg) and 10.9% of their lean mass (-5.7 kg) [14]; in both cases, these values were quantified using DEXA. In individuals with diabetes (the SURPASS-2 trial), the loss of lean mass was 10% with semaglutide (1 mg) and 14% with tirzepatide (15 mg) [15]. There is currently no available data regarding muscle functionality or the prevalence of sarcopenic obesity.

In summary, given the expected weight loss of >10–15% in individuals treated with semaglutide (2.4 mg) or tirzepatide, these patients may experience changes in body composition—specifically a significant reduction in lean mass, particularly skeletal muscle mass—that could increase the risk of sarcopenia. Therefore, we consider it

necessary and a priority to determine the extent of these changes in body composition in patients treated with anti-obesity medications.

2.- HYPOTHESES AND OBJECTIVES

2.1.- Hypothesis: Weight loss in individuals with obesity is associated with a decrease in both fat mass and fat-free mass. When weight loss exceeds 10–15% of total body weight, its impact on skeletal muscle functionality and metabolic adaptation remains uncertain.

2.2.- Objectives:

Primary:

- To determine changes in body composition—assessed via bioelectrical impedance analysis (BIA)—in individuals with obesity treated with pharmacological agents (semaglutide 2.4 mg and tirzepatide) after at least 6 months of treatment.
- To describe changes in body composition in relation to the duration of treatment and the percentage of weight loss (categorized as ≥ 10%, ≥ 15%, and ≥ 20% weight loss).

Secondary:

- To detail weight loss (in terms of fat mass and lean mass), adjusted for age, sex, daily protein intake, and physical activity levels.
- To assess the loss of muscle strength/function, measured using a chair-stand test and handgrip dynamometry.
- To examine the association between the loss of lean mass and muscle functionality.
- To determine the prevalence of sarcopenic obesity.
- To explore, through a sub-analysis, the association between body composition results (obtained via BIA) and other morphological measurements—assessed via abdominal ultrasound—specifically regarding abdominal fat compartments (subcutaneous, preperitoneal, and visceral fat) and the rectus femoris muscle.
- To describe changes in blood pressure, heart rate, and anthropometric data.
- To document both common and uncommon adverse effects. 3.- METHODOLOGY

3.1.- Study type: This is a prospective, observational, multicenter study focused on the pharmacological treatment of obesity in a “real-world” setting. It involves hospital centers associated with members of the Obesity Area of the Spanish Society of Endocrinology and Nutrition (SEEN).

3.2.- Inclusion-exclusion criteria:

Inclusion:

- Subjects of both sexes, between 18-80 years old, with BMI ≥ 30 kg/m2, who start pharmacological treatment for the first time (or who have spent at least 6 months without treatment with GLP1 analogues).

- Patients with weight recovery, after bariatric surgery, with BMI ≥ 30 kg/m2, and increase ≥ 15% from nadir.

- Pharmacological treatment: patient with the capacity to undertake long-term self-funded treatment (minimum 6 months) with semaglutide 2.4 mg/week or tirzepatide 5-10 mg/week.

- Signing of informed consent.

Exclusion:

- Type 1 diabetes

- Type 2 diabetes

- Pregnancy and lactation

- Inability to carry out exercise planning (e.g., disabling arthropathy, advanced COPD, skeletal and muscular alterations, consequences of stroke, etc.) that prevent effective physical exercise (be it aerobic and/or muscle strength).

- Presence of disabling cardiovascular disease (unstable coronary artery disease, NYHA-IV heart failure),

- Advanced deterioration of renal function (GFR < 15 ml/min)

- Advanced liver disease (Child B or higher)

- Major psychiatric illness (depression, eating disorder, psychosis, obsessive-compulsive disorder, personality disorder...).

- People who do not reach the maximum tolerable dose of treatment (considered the maximum dose that does not generate side effects), as long as at least 1 mg of semaglutide and 5 mg of tirzepatide per week are exceeded.

- People who undergo intermittent drug treatment

-People who make a medication change between anti-obesity drugs throughout the observation period.

- Allergy to the components of the selected drug

- History of acute pancreatitis or gastroparesis

- History of MEN-2A or medullary thyroid carcinoma

3.3- Estimation of sample size:

Assuming an effect of 10% loss of lean mass, considering the values of the STEP-I and Surmount-1 study, and with an alpha of 0.05 and a power of 95%, a sample size of 75 people would be necessary (considering at least two pre-post treatment assessments). Since this is a longitudinal study, there may be losses to follow-up which, according to recently published real-life experiences [16], are estimated at 55%, so the final sample would be 116 people. Therefore, each center should include approximately between 6-10 patients who have completed 12 months of follow-up.

4.- Changes in lifestyle and pharmacological treatment:

All patients will be instructed in lifestyle changes, using the usual tools in each workplace. It is recommended to follow a diet with energy restriction of -500 to 1,000 kcal compared to your usual diet or by calculating total energy expenditure and subtracting the same amount of kcal. Special attention will be paid to adequate protein intake (1.2–1.5 g/kg/day, weight adjusted), with 25-30 g of high biological quality protein distributed in each main meal.

The physical exercise approach should include both aerobic exercise (150-200 min/day, at least 3 times a week) and strength exercises (30 min, at least 3 times a week).

The pharmacological treatment will be carried out following the product technical sheet:

• Semaglutide 2.4 mg: start at a dose of 0.25 mg, with dose change escalation every 4 weeks (subcutaneously), until the maximum tolerable dose is reached, with the minimum dose for evaluation being 1 mg/week*. The dose escalation period is estimated between 12-16 weeks.

• Tirzepatide (dose of 2.5-5.0-7.5-10 mg), subcutaneously, administered weekly, with dose escalation every 4 weeks, up to the maximum tolerable dose, with the minimum evaluable dose being 5 mg/week*.

In the case of patients with severe adverse effects and those who do not achieve a weight loss of ≥ 5% in 16 weeks, they will be excluded from the final analysis of the study.

5.- MAIN OUTCOMES

5.1. Primary objectives

5.1.1. Body composition assessment using bioelectrical impedance analysis (BIA), recording raw data for resistance (Rz) and reactance (Xc) at 50 Hz, as well as fat mass, fat-free mass, estimated skeletal muscle mass (SMM), appendicular lean mass (ASM), and phase angle—as provided by the specific BIA device used. Subjects must arrive in a fasted state (8-hour fast), having abstained from caffeine for the previous 24 hours, and with an empty bladder.

The formula by Janssen et al. [18] will be used to estimate skeletal muscle mass (SMM, in kg), and the formula by Ballesteros et al. [19] will be used for appendicular lean mass (ASM).

5.1.2. Demographic and anthropometric data: age, sex, race, weight, height, BMI, blood pressure, heart rate, and waist and calf circumferences (the latter adjusted for BMI). These data will be collected at baseline and after the follow-up period (at 6 and 12 months, as applicable). Based on weight data, the percentage of weight lost and weight-loss categories (≥ 10%, ≥ 15%, ≥ 20%) will be estimated.

5.2. Secondary objectives

5.2.1. Sarcopenia screening: using the SARC-F questionnaire (https://medicalcriteria.com/web/es/sarc-f-sarcopenia/).

5.2.2. Muscle function: assessed via two tests:

a) Dominant-hand dynamometry (using a Jamar dynamometer), with up to 3 measurements taken on the dominant arm.

b) Chair-stand test (5 repetitions), with the time taken to complete the exercise recorded.

5.2.3. Quantitative dietary assessment using 24-hour food records over 3 days (preferably including one weekend day or holiday).

5.2.4 Physical activity assessment (aerobic and resistance), using the IPAQ and RAPA-2 questionnaires. Data converted to MET-hours/week.

5.2.5. Documentation of adverse effects and their severity.

5.2.6. Quality of life questionnaires: IWQOL-Lite (Impact of Weight on Quality of Life) and EuroQoL-5D (a generic quality-of-life instrument).

5.3. Sub-study

- Abdominal ultrasound: Using a linear transducer in a transverse orientation over the abdomen (at the midpoint between the xiphoid process and the umbilicus), subcutaneous, preperitoneal, and visceral fat are measured (in mm).

- Muscle ultrasound: Using a 5.0–10 MHz linear transducer in B-mode (transverse orientation) to determine the thickness, X-axis, and cross-sectional area of the rectus femoris muscle. Adjustments are made for cross-sectional area/height and cross-sectional area/weight.

- All investigators will receive detailed instructions on how to perform the abdominal fat and muscle ultrasound measurements, supported by diagrams or illustrative photographs. Furthermore, all investigators have previously completed a training course organized by the scientific society SEEN.

6.- Patient follow-up:

At least two follow-up assessments will be conducted: a baseline (pre-treatment) assessment and one at 6 months. A 12-month follow-up period is recommended to achieve the maximum efficacy of the drug being evaluated. In other words, 3 follow-up visits are advised, during which all measurements described elsewhere in this protocol will be taken.

Intermediate consultations are recommended to ensure appropriate dose titration, documentation of side effects, adherence to the prescribed diet and physical activity regimen, etc.

Regarding drug management and dose titration, it is recommended to follow the instructions provided in the product's technical data sheet (summary of product characteristics). For common adverse side effects, clinical judgment should be applied; additionally, the visual resources for patients provided in the following Spanish publication [20] may be used.

7.- Planned analysis:

- The variables to be analyzed will be entered into a database created for this purpose, using the SEEN's REDCap resources.

Variables to be recorded and analyzed:

- Personal and anthropometric data (weight, height, BMI, blood pressure, heart rate, and waist and calf circumferences) at baseline and during the follow-up period (6–12 months, as applicable). - Body composition analysis: percentage of fat mass loss, fat-free mass, skeletal muscle mass, and phase angle, assessed at each scheduled consultation (using proprietary data from the specific BIA model employed and/or estimates derived from formulas based on raw resistance, impedance, and anthropometric data):

- Estimation of appendicular lean mass (ALM) = 13.861 + (0.259 x $Height^2/Z$) - (3.983 x sex, where 0 = men and 1 = women).
- Estimation of total skeletal muscle mass (Janssen SMM (kg) = [($Height^2/R$ x 0.401) + (sex x 3.825) + (age x -0.071)] + 5.102).
- Diagnosis of low muscle mass, adjusted for body weight (SMM/weight (kg)) [16]:
  - Class I: 31.5%–37% for men and 22.1%–27.6% for women (1–2 SD);
  - Class II: <31.5% for men and <22.1% for women (< 2 SD).

- Assessment of muscle strength and functionality:

- Changes in muscle strength, evaluated via handgrip dynamometry (using means and percentiles for the Spanish population from Sánchez Torralvo et al. [21]):
  - Cut-off points for impaired muscle strength (via dynamometry): values < 27 kg for men and < 16 kg for women are considered pathological.

- Chair-stand test: 5 repetitions of standing up from and sitting down on a chair:
  - “5-times Sit-to-Stand” test:
  - 11.4 s for ages 60–69;
  - 12.6 s for ages 70–79. years
  - 14.8 s (80–89 years)

-Sub-analysis 1: Baseline and final longitudinal parameters from abdominal fat ultrasound

-Sub-analysis 2: Longitudinal parameters from ultrasound of the rectus femoris muscle (quadriceps)

For the sub-analysis data, only metric measurements will be collected to analyze values at baseline and post-treatment. While reference cut-off points are not yet available for each of the variables assessed via ultrasound, this approach allows us to determine increases or decreases in the measured parameters: the amount of fat and its compartments, as well as the dimensions and volume of the muscle being evaluated.

8.- Statistical analysis:

Statistical analysis will be performed using the SPSSx program (IBM-SPSS software, version 23; Chicago, IL, USA—in Spanish). Quantitative variables will be described as means (SD) or medians (IQR), depending on their distribution. Qualitative variables will be described using absolute and relative frequencies.

Quantitative values will be compared using the independent-samples Student's t-test (for normal distributions) or the Mann-Whitney U test (for non-parametric distributions).

To explore the association of weight loss and fat-free mass loss with other variables (age, sex, race, etc.), binary logistic regression (univariate and multivariate) will be used.

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