Reliability of bioimpedance in the assessment of visceral fat in patients with obesity and metablic syndrome treated with liraglutide for 6 months

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Abstract

BACKGROUND

Metabolic syndrome (MS) and obesity represent a public health problem worldwide and are associated with increased risk of type-II diabetes mellitus and cardiovascular disease. Bioimpedance analysis is a practical and effective way of evaluating body composition, especially with regard to abdominal fat. Liraglutide, the first GLP-1 analog approved for treatment of obesity, reduces body weight and improves cardiometabolic parameters.

METHODS

Prospective study on 103 adult obese patients with MS followed for 6 months. The treatment group (n = 57) received liraglutide at 3 mg/day, while the control group (n = 43) received sibutramine at 15 mg/day. All patients were submitted to bioimpedance analysis, physical examination and lab testing at baseline and at 6 months.

RESULTS

A greater reduction was observed in the treatment group with regard to fat mass (-10.5 [-14.3; -7.7] *vs* -7.65 [-10.5; -5.3], $p = 0.001$) and abdominal circumference (AC) (-13 [-16; -9] *vs* -6 [-9; -4], $p < 0.001$). In the bioimpedance analysis, liraglutide was associated with a greater reduction in the fat mass of both arms and the trunk ($p < 0.05$). AC and truncal fat mass were strongly correlated (*rho* = 0.531, $p < 0.001$) in the treatment group.

CONCLUSION

Treatment with liraglutide at 3 mg/day for 6 months efficiently promoted weight loss and improved bioimpedance, cardiometabolic and inflammatory parameters in obese MS patients. Bioimpedance analysis was found to be a practical and reliable way of quantifying loss of visceral fat in this patient population.

Introduction

Obesity is a complex and multifactorial chronic disorder frequently refractory to treatment and prediposing towards the development of cardiometabolic conditions, such as,cardiovascular disease (CD), type-II diabetes mellitus (DM-II), systemic arterial hypertension (SAH), metabolic syndrome (MS) and other comorbidities [1, 2].

MS, a systemic proinflammatory condition, involves a set of complex metabolic changes, such as insulin resistance, central obesity, SAH, hypertriglyceridemia and reduced HDL cholesterol levels. Due to its close association with CD and DM-II, MS is considered a major public health problem worldwide [3–6].

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist 97% similar to native GLP-1[7] secreted by intestinal L-cells at the level of the distal jejunum, ileum and colon in response to the ingestion of carbohydrates, lipids and mixed food [8, 9]. It reduces blood sugar levels, inhibits glucagon secretion, increases insulin secretion, suppresses the appetite and calorie intake, retards gastric emptying, and enhances sensitivity to insulin [10, 11].

Due to its direct implication for the metabolism, body composition should be determined before initiating treatment of obesity [12]. This may be done in the clinical setting by bioimpedance analysis, a safe and simple procedure which provides timely results based on the measurement of electrical resistance in different body tissues[12].

Morlino *et al*. [13] used bioimpedance analysis to study the prevalence of sarcopenia in breast cancer patients. In their study, sarcopenia was detected in 13.9% in relation to controls, and sarcopenic patients were found to have significantly less fat-free body mass. Likewise, using bioimpedance analysis as a screening tool, Peppa *et al*. [14] observed a greater loss of lean body mass in postmenopausal women with sarcopenia. To our knowledge, no previous study has analyzed the bioimpedance parameters of this particular patient population.

In this study, we evaluated the effect of 6 months of treatment with liraglutide on the clinical, laboratory and bioimpedance findings of adult patients diagnosed with obesity and MS, compared to a control group.

Methods

Patients

This prospective, longitudinal study of patient records was conducted at a private clinic in Fortaleza (Northeastern Brazil) from December 2021 to January 2023. The sample included 103 adults of both sexes aged ≥ 21 years, with obesity (BMI ≥ 30 kg/m^2) and a diagnosis of MS based on the “Harmonizing the Metabolic Syndrome” criteria (IDF/NHLBI/AHA/WHO/IAS/IASO) adjusted for South Americans [15]. Over a period of 6 months, 57 patients received liraglutide at 3 mg/day s.c. (treatment group) and 46 received sibutramine at 15 mg/day p.o. (control group). All patients were submitted to bioimpedance analysis, physical examination and lab testing at baseline and at 6 months.

Liraglutide is marketed under the trade name Saxenda by Novo Nordisk A/S (Bagsværd, Denmark) and Novo Nordisk Pharmaceutical Industries LP (Clayton, USA). Neither company was involved in this study, or supported it in any manner, or had access to the study data. The compound, a GLP-1 receptor agonist, reduces the appetite and, consequently, reduces food ingestion, promoting weight loss. The drug can cause nausea, vomiting, diarrhea, constipation, loss of appetite, dyspeptic symptoms, sensation of weakness, injection site reactions (hematoma, irritation, rash) and dizziness, among others [16].

Sibutramine hydrochloride monohydrate is an anti-obesity drug which acts primarily through its active metabolites monodesmethyl (M1) and didesmethyl (M2) by effectively blocking the recapture of serotonin (5-hydroxytryptamine), norepinephrine and dopamine. The compound inhibits the appetite by promoting a sensation of satiety and diminishes weight loss-induced decline in energy expenditure [17]. The adverse effects include constipation, dry mouth and insomnia (up to 10% of cases), and palpitations, tachycardia, headache, increased blood pressure and sweating (less than 10% of cases). The brand Biomag was used in this study. The manufacturer (Achè Laboratórios Farmacêuticos S.A.) did not support this study in any manner and had no access to the study data.

The exclusion criteria were age ≤ 21 years, BMI ≤ 30 mg/m^2, MS diagnosed by criteria other than the "Harmonizing the Metabolic Syndrome" criteria adjusted for South Americans [15], hypothyroidism, depression, use of antidepressants, pregnancy, breastfeeding, family history of hypersensitivity to liraglutide or sibutramine, pancreatitis, multiple endocrine neoplasia, and family history of medullary carcinoma of the thyroid. Patients with poorly controlled hypertension and/or previous cerebrovascular disease were excluded from the control (sibutramine) group.

The study complied with the tenets of the Declaration of Helsinki [18], and all patients gave their informed written consent prior to inclusion in the study protocol. The protocol was uploaded to 'Plataforma Brasil' and approved under CAAE #64954722.7.0000.5052.

Study protocol

All patients were submitted to clinical and anthropometric evaluations, including abdominal circumference (AC), arterial pressure and lab tests, at baseline and after 6 months of protocol. Patients in the treatment group were instructed in the proper daily subcutaneous administration of liraglutide (preferably in the morning, in the abdomen or the upper inner arm) at an initial dose of 0.6 mg/day. The dose was raised by 0.6 mg at weekly intervals until reaching 3 mg/day (0.6→1.2→1.8→2.4→3 mg/day). The control group received sibutramine at 15 mg/day p.o. in the morning. All patients were instructed to reduce their calorie ingestion and encouraged to perform physical activity.

Clinical, anthropometric and laboratory evaluations

During the clinical examination, a standardized questionnaire was administered to collect personal information on current health, food habits, physical activity, current and previous treatments, comorbidities, and family history of obesity, diabetes and SAH.

AC was measured with a with a tape positioned horizontally halfway between the iliac crest and the last rib.

Arterial pressure was measured with a previously calibrated sphygmomanometer, using a cuff compatible with the patient's arm circumference (cuff size 12 x 23 for 25–34 cm; cuff size 16 x 32 for 35–45 cm). After resting for at least 5 min in a quiet room, arterial pressure was measured twice at a

minimum interval of 2 min, as proposed by the 2018 ESH/ESC guidelines for the management of SAH [19].

Fat mass and lean mass were quantified for all body segments (arms, legs, trunk) using an InBody 270 tetrapolar bioimpedance [20] device manufactured in South Korea and licensed in Brazil by Anvisa under #80051870004. The percentage of body fat (BF%), weight and BMI were registered with the same device.

The bioimpedance device features 8 contact points capable of collecting 10 measurements from each body segment (right arm, left arm, right leg, left leg, trunk) using 2 different frequencies (20 KHz and 100 KHz) and a current of 250 μA (Table 1). [21]

Table 1

Bioimpedance parameters registered in the study.

Parameter	Abbreviation
Total weight	TWT
Fat mass in the right arm	FMA-R
Fat mass in the left arm	FMA-L
Fat mass in the trunk	FMT
Fat mass in the right leg	FML-R
Fat mass in the left leg	FML-L
Lean mass in the right arm	LMA-R
Lean mass in the left arm	LMA-L
Lean mass in the trunk	LMT
Lean mass in the right leg	LML-R
Lean mass in the left leg	LML-L
Body-mass index	BMI
Percentage of body fat	BF%
Waist-to-hip ratio	WHR

For the best results, patients were recommended to abstain from food and drink two hours before the evaluation, void the bladder immediately before, not to practice physical activity or use the sauna on the day of the evaluation, and not to be menstruating. Evaluations were conducted at room temperature (20–25℃). Height was measured with a stadiometer.

Blood was collected after 12 hours of fasting and 72 hours of abstention from alcohol and heavy exercise. The lab parameters included fasting glycemia, insulin, glycated hemoglobin, HOMA-IR, total cholesterol, HDL, LDL, triglycerides, uric acid, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

ESR (mm/hr) was measured in whole blood using the automated Westergreen method. CRP (mg/dL) was measured in serum on nephelometry (Dade-Behring® BNII). Serum levels of glucose (mg/dL) were determined with the glucose-oxidase enzyme method, while serum levels of urea (mg/dL) were estimated with the UV-kinetic method. Using the kinetic method without deproteinization, we quantified serum creatinine (mg/dL), while enzymatic colorimetry was employed to determine triglycerides (mg/dL), total cholesterol (mg/dL) and uric acid (mg/dL). To obtain the lipid profile (mg/dL), we submitted serum samples to calorimetry (Wiener®CMD 800i; Konelab®60i). Serum was also used for the estimation of high-density lipoprotein (HDL) (mg/dL) and low-density lipoproteine (LDL) (mg/dL) on calorimetry (calculated with the Fredwald formula CT = HDL + LDL + TG/5 whenever triglycerides were < 300 mg/dL). Finally, the insulin concentration in whole blood (μU/mL) was estimated on immunofluorometry and insulin resistence was defined by the HOMA-IR index of the top quartile of a non-diabetic population.

Diagnosis of metabolic syndrome

MS was classified according to the “Harmonizing the Metabolic Syndrome” statement (IDF/NHLBI/AHA/WHO/IAS/IASO) [15], which requires the presence of 3 of the 5 criteria below:

- Increase in AC using values adjusted for South Americans (≥ 90 for men; ≥80 for women)
- TG ≥ 150 mg/dL, or receiving treatment
- HDL ≤ 40 mg/dL for men and ≤ 50 mg/dL for women, or receiving treatment
- Arterial pressure ≥ 130/≥85 mmHg, or use of antihypertensive medication
- Fasting glycemia ≥ 100 mg/dL, or diagnosis of DM.

Statistical analysis

Categorical variables were expressed as absolute values and relative frequency (%). The chi-square test was used to identify associations between categorical variables. The normality of distribution of the continuous variables was verified with the Kolmogorov-Smirnov test. Asymmetry was evaluated based on histograms and Q-Q graphs. Normal data were expressed as means ± standard deviation, while non-normal data were expressed as medians and interquartile range.

Pairwise comparisons of continuous variables of independent groups were made with Student’s *t* test (nomal distribution) or the Mann-Whitney test (non-normal distribution). Pairwise comparisons of dependent groups were made with the paired *t* test (nomal distribution) or the Wilcoxon test (non-normal distribution). Finally, quantitative variables were submitted to correlation analysis using Spearman’s non-parametric correlation analysis (*rho* coefficient).

All statistical analyses were performed with the software SPSS for Macintosh v. 23 (Armonk, NY: IBM Corp.). The level of statistical significance was set at 5% ($p < 0.05$).

Results

Our sample of MS patients (n = 103) was segregated into a treatment group (n = 57, liraglutide 3 mg/day) and a control group (n = 46, sibutramine 15 mg/day). Prior to initiating the protocol, the groups were compared and found to be statistically similar with regard to age ($p = 0.480$) and sex ($p = 0.306$), but almost all the anthropometric variables were higher in the treatment group than in the control group: Total weight 106 ± 20 kg *vs* 91 ± 18 kg ($p < 0.001$), fat mass 35.1 ± 12.1 kg *vs* 29.4 ± 10 kg ($p < 0.001$), lean mass 32.1 ± 7.7 kg *vs* 28.8 ± 8 kg ($p = 0.033$), BMI 37.5 ± 5.1 kg/m^2 *vs* 33 ± 3.7 kg/m^2 ($p < 0.001$), AC 120.6 ± 15.7 cm *vs* 106.2 ± 13.6 cm ($p < 0.001$), and WHR 1.1 ± 0.1 *vs* 1 ± 0.1 ($p = 0.003$) (Table 2).

Table 2

Baseline findings for the treatment group (liraglutide) and the control group (sibutramine).

	Groups		
	Control (n = 46)	**Liraglutide (n = 57)**	***p****
Clinical findings			
Sex			0.306
Female	26 (56.5)	24 (42.1)	
Male	20 (43.5)	33 (57.9)	
Age (years)	45 ± 10	43 ± 11	0.480
SAP (mmhg)	121.2 ± 6.3	129.8 ± 11.8	0.000
DAP (mmhg)	79.9 ± 4.4	83.3 ± 7	0.004
Anthropometric findings			
Body weight (Kg)	91 ± 18	106 ± 20	0.000
Muscle mass (Kg)	28.8 ± 8	32.1 ± 7.7	0.033
Fat mass (Kg)	29.4 ± 10	35.1 ± 12.1	0.000
BMI (Kg/m^2)	33 ± 3.7	37.5 ± 5.1	0.000
AC (cm)	106.2 ± 13.6	120.6 ± 15.7	0.000
WHR	1 ± 0.1	1.1 ± 0.1	0.003
Bioimpedance			
BF%	41.3 ± 7.9	44.2 ± 7.9	0.071
LMA-R (Kg)	2.7 ± 1	3.3 ± 1	0.004

Continuous variables expressed as mean ± standard deviation or median and interquartile range (in parenthesis). Categorical variables were expressed as absolute values and percentages (in parenthesis). Continuous variables were compared with Student's *t* test or the Mann-Whitney test. Categorical variables were analyzed with the chi-square test.

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body-mass index; AC = abdominal circumference; WHR = waist-to-hip ratio; BF%=percentage of body fat; LMA-R = lean mass in the right arm; LMA-L = lean mass in the left arm; LMT = lean mass in the trunk; LML-R = lean mass in the right leg; LML-L = lean mass in the left leg; FMA-R = fat mass in the right arm; FMA-L = fat mass in the left arm; FMT = fat mass in the trunk; FML-R = fat mass in the right leg; FML-L = fat mass in the left leg; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TGO = aspartate aminotransferase, TGP = alanine aminotransferase, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein; TSH = thyroid-stimulating hormone.

	Groups		
	Control (n = 46)	Liraglutide (n = 57)	*p**
Clinical findings			
LMA-L (Kg)	2.7 ± 1	3.3 ± 1	0.007
LMT (Kg)	20.2 ± 7.2	23.8 ± 6.9	0.010
LML-R (Kg)	7.1 ± 2	8.1 ± 2.1	0.013
LML-L (Kg)	7.1 ± 2.1	8.1 ± 2.1	0.016
FMA-R (Kg)	3 ± 1.4	4.3 ± 1.7	0.000
FMA-L (Kg)	2.9 ± 1.3	4.3 ± 1.7	0.000
FMT (Kg)	19.9 ± 5.4	25.1 ± 5.5	0.000
FML-R (Kg)	5.6 ± 1.6	7 ± 2.1	0.001
FML-L (Kg)	5.7 ± 1.6	7 ± 2.1	0.001
Laboratory findings			
Fasting glycemia (mg/dL)	96.2 ± 9.8	99 ± 16	0.287
Insulin (μU/mL)	15.6 (9.8–21)	20.2 (12.4–27)	0.018
HOMA-IR	3.49 (2.25–4.96)	5.15 (3.2–6.7)	0.013
Total cholesterol (mg/dL)	194.4 ± 51.2	196 ± 43.3	0.863
LDL (mg/dL)	129.4 ± 40.4	124.3 ± 40.4	0.525
HDL (mg/dL)	45.3 ± 16.3	49.7 ± 19.2	0.224
Triglycerides (mg/dL)	197 ± 70.2	204.8 ± 74.5	0.590
TGO (U/L)	27 (23–32)	28 (21–36)	0.513

Continuous variables expressed as mean ± standard deviation or median and interquartile range (in parenthesis). Categorical variables were expressed as absolute values and percentages (in parenthesis). Continuous variables were compared with Student's *t* test or the Mann-Whitney test. Categorical variables were analyzed with the chi-square test.

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body-mass index; AC = abdominal circumference; WHR = waist-to-hip ratio; BF%=percentage of body fat; LMA-R = lean mass in the right arm; LMA-L = lean mass in the left arm; LMT = lean mass in the trunk; LML-R = lean mass in the right leg; LML-L = lean mass in the left leg; FMA-R = fat mass in the right arm; FMA-L = fat mass in the left arm; FMT = fat mass in the trunk; FML-R = fat mass in the right leg; FML-L = fat mass in the left leg; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TGO = aspartate aminotransferase, TGP = alanine aminotransferase, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein; TSH = thyroid-stimulating hormone.

	Groups		
	Control (n = 46)	**Liraglutide (n = 57)**	***p****
Clinical findings			
TGP (U/L)	27 (22–34)	39 (24–66)	0.026
Urea (mg/dL)	33.7 ± 7.9	31.1 ± 8.7	0.122
Creatinine (mg/dL)	0.85 ± 0.18	0.86 ± 0.18	0.773
Vitamin D (ng/mL)	31 ± 12.5	26.1 ± 8.6	0.023
ESR (mm/h)	12 (9–19)	14 (9–19)	0.468
CRP (mg/dL)	0.29 (0.08–0.85)	0.73 (0.3–1.41)	0.002
TSH (U/L)	2.13 ± 0.97	1.87 ± 0.77	0.144
Glycated hemoglobin (%)	5.4 ± 0.5	5.8 ± 1.1	0.060
Uric acid (mg/dL)	5.3 ± 1.3	5.9 ± 1.8	0.052

Continuous variables expressed as mean ± standard deviation or median and interquartile range (in parenthesis). Categorical variables were expressed as absolute values and percentages (in parenthesis). Continuous variables were compared with Student's *t* test or the Mann-Whitney test. Categorical variables were analyzed with the chi-square test.

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body-mass index; AC = abdominal circumference; WHR = waist-to-hip ratio; BF%=percentage of body fat; LMA-R = lean mass in the right arm; LMA-L = lean mass in the left arm; LMT = lean mass in the trunk; LML-R = lean mass in the right leg; LML-L = lean mass in the left leg; FMA-R = fat mass in the right arm; FMA-L = fat mass in the left arm; FMT = fat mass in the trunk; FML-R = fat mass in the right leg; FML-L = fat mass in the left leg; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TGO = aspartate aminotransferase, TGP = alanine aminotransferase, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein; TSH = thyroid-stimulating hormone.

Likewise, bioimpedance variables were significantly higher in the treatment group than in the control group, with the exception of BF% (44.2 ± 7.9 *vs* 41.3 ± 7.9; $p = 0.071$). The remaining variables were: LMA-R 3.3 ± 1 kg *vs* 2.7 ± 1 kg ($p = 0.004$), LMA-L 3.3 ± 1 kg *vs* 2.7 ± 1 kg ($p = 0.007$), LMT 23.8 ± 6.9 kg *vs* 20.2 ± 7.2 kg ($p = 0.010$), LML-R 8.1 ± 2.1 kg *vs* 7.1 ± 2 kg ($p = 0.013$), LML-L 8.1 ± 2.1 kg *vs* 7.1 ± 2.1 kg ($p = 0.016$), FMA-R 4.3 ± 1.7 kg *vs* 3 ± 1.4 kg ($p = 0.000$), FMA-L 4.3 ± 1.7 kg *vs* 2.9 ± 1.3 kg ($p = 0.000$), FMT 25.1 ± 5.5 kg *vs* 19.9 ± 5.4 kg ($p = 0.000$), FML-R 7 ± 2.1 kg *vs* 5.6 ± 1.6 kg ($p = 0.001$), and FML-L 7 ± 2.1 kg *vs* 5.7 ± 1.6 kg ($p = 0.001$).

At baseline, the treatment group also differed from the control group with regard to laboratory variables, including higher blood insulin levels: 20.2 [12.4–27] μU/mL *vs* 15.6 [9.8–21] μU/mL ($p = 0.015$), greater

insulin resistance: 5.15 [3.2–6.7] *vs* 3.49 [2.25–4.96] ($p = 0.013$), and higher CRP levels: 0.73 [0.3–1.41] mg/dL *vs* 0.29 [0.08–0.85] mg/dL ($p = 0.002$) (Table 2).

Treatment with liraglutide at 3 mg/day for 6 months significantly improved all clinical and anthropometric variables ($p < 0.001$). Some bioimpedance variables also improved significantly in the treatment group ($p < 0.05$), including: BF% 44.2 ± 7.9 *vs* 38.1 ± 9.3 ($p < 0.001$), FMA-R 4.3 ± 1.7 kg *vs* 3.2 ± 1.6 kg ($p < 0.001$), FMA-L 4.3 ± 1.7 kg *vs* 3.3 ± 1.6 kg ($p < 0.001$), and FMT 25.1 ± 5.5 kg *vs* 17.9 ± 5.1 kg ($p < 0.001$) (Table 3).

Table 3
Clinical, anthropometric and bioimpedance findings at baseline and after 6 months of treatment with liraglutide.

	Liraglutide		
	Baseline	**6 months**	***p****
Clinical parameters			
SAP (mmhg)	129.8 ± 11.8	111.5 ± 9.1	< 0.001
DAP (mmhg)	83.3 ± 7	71.9 ± 8.3	< 0.001
Anthropometric parameters			
Body weight (Kg)	106 ± 20	94 ± 18	< 0.001
Muscle mass (Kg)	33.4 ± 7.9	32.1 ± 7.7	< 0.001
Fat mass (Kg)	46.9 ± 12.4	35.1 ± 12.1	< 0.001
BMI (Kg/m^2)	37.5 ± 5.1	32.8 ± 5	< 0.001
AC (cm)	120.6 ± 15.7	107.6 ± 13.7	< 0.001
WHR	1.07 ± 0.06	0.99 ± 0.06	< 0.001
Bioimpedance			
BF%	44.2 ± 7.9	38.1 ± 9.3	< 0.001
LMA-R (Kg)	3.3 ± 1	3.0 ± 1	< 0.001
LMA-L (Kg)	3.3 ± 1	3.0 ± 1	< 0.001
LMT (Kg)	23.8 ± 6.9	22.9 ± 7	0.006
LML-R (Kg)	8.1 ± 2.1	7.7 ± 2	< 0.001
LML-L (Kg)	8.1 ± 2.1	7.7 ± 2	< 0.001
FMA-R (Kg)	4.3 ± 1.7	3.2 ± 1.6	< 0.001
FMA-L (Kg)	4.3 ± 1.7	3.3 ± 1.6	< 0.001
FMT (Kg)	25.1 ± 5.5	17.9 ± 5.1	< 0.001

Continuous variables were compared with the pared *t* test and expressed as mean ± standard deviation. SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body-mass index; AC = abdominal circumference; WHR = waist-to-hip ratio; BF%=percentage of body fat; LMA-R = lean mass in the right arm; LMA-L = lean mass in the left arm; LMT = lean mass in the trunk; LML-R = lean mass in the right leg; LML-L = lean mass in the left leg; FMA-R = fat mass in the right arm; FMA-L = fat mass in the left arm; FMT = fat mass in the trunk; FML-R = fat mass in the right leg; FML-L = fat mass in the left leg.

	Liraglutide		
	Baseline	**6 months**	***p****
Clinical parameters			
FML-R (Kg)	7 ± 2.1	5.8 ± 1.9	< 0.001
FML-L (Kg)	7 ± 2.1	5.8 ± 1.9	< 0.001

Continuous variables were compared with the pared *t* test and expressed as mean ± standard deviation. SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body-mass index; AC = abdominal circumference; WHR = waist-to-hip ratio; BF%=percentage of body fat; LMA-R = lean mass in the right arm; LMA-L = lean mass in the left arm; LMT = lean mass in the trunk; LML-R = lean mass in the right leg; LML-L = lean mass in the left leg; FMA-R = fat mass in the right arm; FMA-L = fat mass in the left arm; FMT = fat mass in the trunk; FML-R = fat mass in the right leg; FML-L = fat mass in the left leg.

In the treatment group, the following laboratory variables improved significantly: fasting gycemmia ($p < 0.001$), glycated hemoglobin ($p < 0.001$), blood insulin ($p < 0.001$), HOMA-IR ($p < 0.001$), total cholesterol ($p < 0.001$), LDL ($p < 0.001$), and triglycerides ($p < 0.001$). Improvement was also observed for the inflammatory parameters ESR ($p < 0.001$) and CRP ($p = 0.007$) (Table 4).

Table 4
Laboratory findings at baseline and after 6 months of treatment with liraglutide.

	Liraglutide		
	Baseline	**6 months**	***p****
Laboratory parameters			
Fasting glycemia (mg/dL)	99 ± 16	87.3 ± 9	< 0.001
Insulin (μU/mL)	20.2 (12.4–27)	10.7 (7.2–16)	< 0.001
HOMA-IR	5.15 (3.2–6.7)	2.27 (1.62–3.47)	< 0.001
Total cholesterol (mg/dL)	196 ± 43.3	172.6 ± 33.2	< 0.001
LDL (mg/dL)	124.3 ± 40.4	97.3 ± 30.6	< 0.001
HDL (mg/dL)	49.7 ± 19.2	54.5 ± 18.3	0.161
Triglycerides (mg/dL)	204.8 ± 74.5	109.2 ± 44.1	< 0.001
TGO (U/L)	28 (21–36)	23 (19–27)	0.003
TGP (U/L)	39 (24–66)	30 (20–40)	0.003
Urea (mg/dL)	31.1 ± 8.7	31.6 ± 8.4	0.635
Creatinine (mg/dL)	0.86 ± 0.18	0.88 ± 0.18	0.202
Vitamin D (ng/mL)	26.1 ± 8.6	31.7 ± 8.2	0.001
ESR (mm/h)	14 (9–19)	8 (6–11)	< 0.001
CRP (mg/dL)	0.73 (0.3–1.41)	0.45 (0.2–0.68)	0.007
TSH (U/L)	1.87 ± 0.77	1.75 ± 0.64	0.285
Glycated hemoglobin (%)	5.8 ± 1.1	5.3 ± 0.4	< 0.001
Uric acid (mg/dL)	5.9 ± 1.8	5 ± 1.3	< 0.001

Continuous variables were compared with the paired *t* test or the Mann-Whitney test and expressed as mean ± standard deviation or median and interquartile range (in parenthesis). HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TGO = aspartate aminotransferase, TGP = alanine aminotransferase, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein; TSH = thyroid-stimulating hormone

Subsequently, the treatment group and the control group were compared with regard to improvements in clinical, anthropometric, bioimpedance and laboratory parameters. Weight loss (5% and 10%) was similar in the two groups ($p = 1.00$ and $p = 0.322$, respectively), but SAP and DAP were significantly lower in the treatment group than in the control group ($p < 0.05$) (Table 5). A number of anthropometric variables also

decreased significantly more in the treatment group, such as total weight (-12.3 [-16.2; -9.3] *vs* -9.65 [-12.3; -7], $p = 0.009$), fat mass (-10.5 [-14.3; -7.7] *vs* -7.65 [-10.5; -5.3], $p = 0.001$), BMI (-4.6 [-5.9; -3.5] vs -3.6 [-4.6; -2.5], $p = 0.001$), AC (13 [-16; -9] *vs* -6 [-9; -4], $p < 0.001$) and WHR (-0.08 [-0.1; -0.06] *vs* -0.06 [-0.08; -0.04], $p = 0.032$) (Table 5). The following bioimpedance variables decreased significantly more in the treatment group: FMA-R (-1 [-1.6; -0.6] *vs* -0.7 [-1; -0.5], $p = 0.034$), FMA-L (-1 [-1.6; -0.6] *vs* -0.7 [-1; -0.4], $p = 0.037$), FMT (-7.2 [-9.4; -5.2] vs -3.45 [-5.2; -2.5], $p < 0.001$) (Table 5).

Table 5
Comparison of bioimpedance and anthropometric variables in the treatment group (liraglutide) and the control group (sibutramine).

	Groups		
Variation (Post-Pre-treatment)	**Controls (n = 46)**	**Liraglutide (n = 57)**	p*
Loss of 5% of baseline weight			1.000
No	3 (6.5)	4 (7)	
Yes	43 (93.5)	53 (93)	
Loss of 10% of baseline weight			0.322
No	18 (39.1)	17 (29.8)	
Yes	28 (60.9)	40 (70.2)	
Clinical parameters			
SAP (mmhg)	-2.5 (-10; 0)	-20 (-30; -10)	0.000
DAP (mmhg)	0 (-10; 0)	-10 (-20; -5)	0.000
Anthropometric parameters			
Body weight (Kg)	-9.65 (-12.3; -7)	-12.3 (-16.2; -9.3)	0.009
Muscle mass (Kg)	-1.1 (-1.8; 0)	-1.1 (-2.2; 0)	0.557
Fat mass (Kg)	-7.65 (-10.5; -5.3)	-10.5 (-14.3; -7.7)	0.001
BMI (Kg/m^2)	-3.6 (-4.6; -2.5)	-4.6 (-5.9; -3.5)	0.001
AC (cm)	-6 (-9; -4)	-13 (-16; -9)	0.000
WHR (cm)	-0.06 (-0.08; -0.04)	-0.08 (-0.1; -0.06)	0.032
Bioimpedance			
BF%	-4.95 (-7.2; -3)	-5.7 (-8.4; -3.5)	0.266
LMA-R (Kg)	-0.2 (-0.4; 0)	-0.2 (-0.4; 0)	0.733
LMA-L (Kg)	-0.2 (-0.3; -0.1)	-0.2 (-0.4; 0)	0.825
LMT (Kg)	-0.7 (-1.3; 0)	-1 (-1.9; 0)	0.302

Continuous variables were compared with the Mann-Whitney test and expressed as median and interquartile range.SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body-mass index; AC = abdominal circumference; WHR = waist-to-hip ratio; BF%=percentage of body fat; LMA-R = lean mass in the right arm; LMA-L = lean mass in the left arm; LMT = lean mass in the trunk; LML-R = lean mass in the right leg; LML-L = lean mass in the left leg; FMA-R = fat mass in the right arm; FMA-L = fat mass in the left arm; FMT = fat mass in the trunk; FML-R = fat mass in the right leg; FML-L = fat mass in the left leg.

	Groups		
LML-R (Kg)	-0.3 (-0.4; 0)	-0.4 (-0.6; 0)	0.095
LML-L (Kg)	-0.3 (-0.5; 0)	-0.3 (-0.7; -0.1)	0.085
FMA-R (Kg)	-0.7 (-1; -0.5)	-1 (-1.6; -0.6)	0.034
FMA-L (Kg)	-0.7 (-1.1; -0.4)	-1 (-1.5; -0.6)	0.037
FMT (Kg)	-3.45 (-5.2; -2.5)	-7.2 (-9.4; -5.2)	0.000
FML-R (Kg)	-1.1 (-1.5; -0.7)	-1.2 (-1.6; -0.8)	0.640
FML-L (Kg)	-1.1 (-1.6; -0.7)	-1.1 (-1.6; -0.8)	0.705
Continuous variables were compared with the Mann-Whitney test and expressed as median and interquartile range.SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body-mass index; AC = abdominal circumference; WHR = waist-to-hip ratio; BF%=percentage of body fat; LMA-R = lean mass in the right arm; LMA-L = lean mass in the left arm; LMT = lean mass in the trunk; LML-R = lean mass in the right leg; LML-L = lean mass in the left leg; FMA-R = fat mass in the right arm; FMA-L = fat mass in the left arm; FMT = fat mass in the trunk; FML-R = fat mass in the right leg; FML-L = fat mass in the left leg.			

Since the reduction in AC and FMT was significantly greater in the treatment group than in the control group, we tested for a possible association between the two parameters and found a strong correlation ($rho = 0.531$; $p < 0.001$) in the treatment group (Fig. 1).

Discussion

This is to our knowledge the first study to evaluate the ability of bioimpedance analysis to assess body fat in obese MS patients treated with liraglutide for 6 months. The adopted bioimpedance parameters (especially fat mass in the trunk and arms) did in fact improve in our sample of patients. We also found liraglutide at 3 mg/day to efficiently improve clinical and laboratory findings in obese MS patients, matching the results of other studies on weight loss and cardiometabolic profile in this patient population.

The inclusion of age- and sex-matched controls allowed us to reliably establish whether the use of a GLP-1 analog can significantly modify the bioimpedance variables in a specific group of patients. In addition, our comprehensive clinical and laboratory evaluations at baseline and at 6 months made it possible to study the accuracy of bioimpedance analysis in the management of MS.

Six months of liraglutide treatment led to reductions in SAP and DAP and to improvements in anthropometric variables (reductions in total weight, fat mass, BMI and AC), as observed by several other authors[22–28]. In support of our findings, a double-blind study involving 3731 patients reported weight loss and a reduction of glycemia and cardiometabolic risk factors after 52 weeks of treatment with

liraglutide at 3 mg/day [28], while another study comparing liraglutide to placebo and orlistat found the metabolic profile to have improved most in the liraglutide group, suggesting the compound can significantly reduce insulin resistance and glycemia and promote weight loss [29].

Among the laboratory variables, improvement was observed for fasting glycemia, glycated hemoglobin, insulin resistance, lipid profile, and inflammatory markers, indicating a better overall metabolic and inflammatory profile[2, 24, 27, 29]. Our findings point to a significantly improved cardiometabolic and inflammatory profile after 6 months of treatment, whereas other studies have generally relied on longer follow-up periods (~ 1 year)[27]. Thus, our study suggests that liraglutide can promote weight loss and glycemia reduction in less time than previously believed.

Improvement in anthropometric and bioimpedance variables was significantly greater in the treatment (liraglutide) group than in the control (sibutramine) group, as shown by the findings for total weight, fat mass, BMI, AC, WHR, FMT, FMA-R and FMA-L. In a study by Carmina *et al.*, the risk of cardiovascular and metabolic changes was higher for peripheral obesity than for central obesity [30]. Visceral adipose tissue is now known to be a key component of MS; therefore, AC is an important parameter in clinical practice for improving the stratification of cardiometabolic risk. However, a high AC value alone is not enough to adequately assess the accumulation of abdominal fat [4, 31], making it necessary to adopt more accurate methods of quantification, capable of monitoring treatment and preventing cardiac complications.

One such method is bioimpedance analysis, which has been validated for the assessment of body composition [32–34]. The method can evaluate fat mass in several body compartments and has been shown to perform quite well compared to more costly methods, such as computed tomography [35]. In this study, bioimpedance analysis effectively assessed different body segments, showing truncal fat loss to be correlated with reductions in AC and abdominal fat loss. Interestingly, another Brazilian study evaluated the reliability of bioimpedance and indirect calorimetry in the measurement of the resting metabolic rate of 40 women with MS over a period of 6 months, and concluded that, compared to indirect calorimetry, bioimpedance analysis is a practical and time-saving method which does not require prolonged fasting in order to produce reliable results [36].

The observed reduction in AC and FMT in patients treated with liraglutide implies a reduction in visceral fat—the main cardiovascular risk factor in MS[4, 31]. This correlation would appear to validate bioimpedance analysis as an adequate assessment of abdominal fat.

The limitations of this study included the short follow-up period (6 months) and the relatively small sample of patients. Moreover, a multiple regression analysis might have helped identify factors independently influencing the study variables.

In conclusion, treatment with liraglutide at 3 mg/day for 6 months efficiently promoted weight loss and improved bioimpedance, cardiometabolic and inflammatory parameters in obese MS patients. Bioimpedance analysis was found to be a practical and reliable way of quantifying loss of visceral fat in

this patient population. Studies on larger samples and with longer follow-up periods are necessary to confirm and extrapolate our findings.

Declarations

AUTHOR CONTRIBUTIONS

Conceptualization: FC and CEMR Analysis: FC and CEMR Writing-Original draft: FC and CEMR Writing-review and etiting: FC and CEMR.

COMPETING INTERESTS

The authors declare no competing interests

Conflicts of interest

None

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Figures

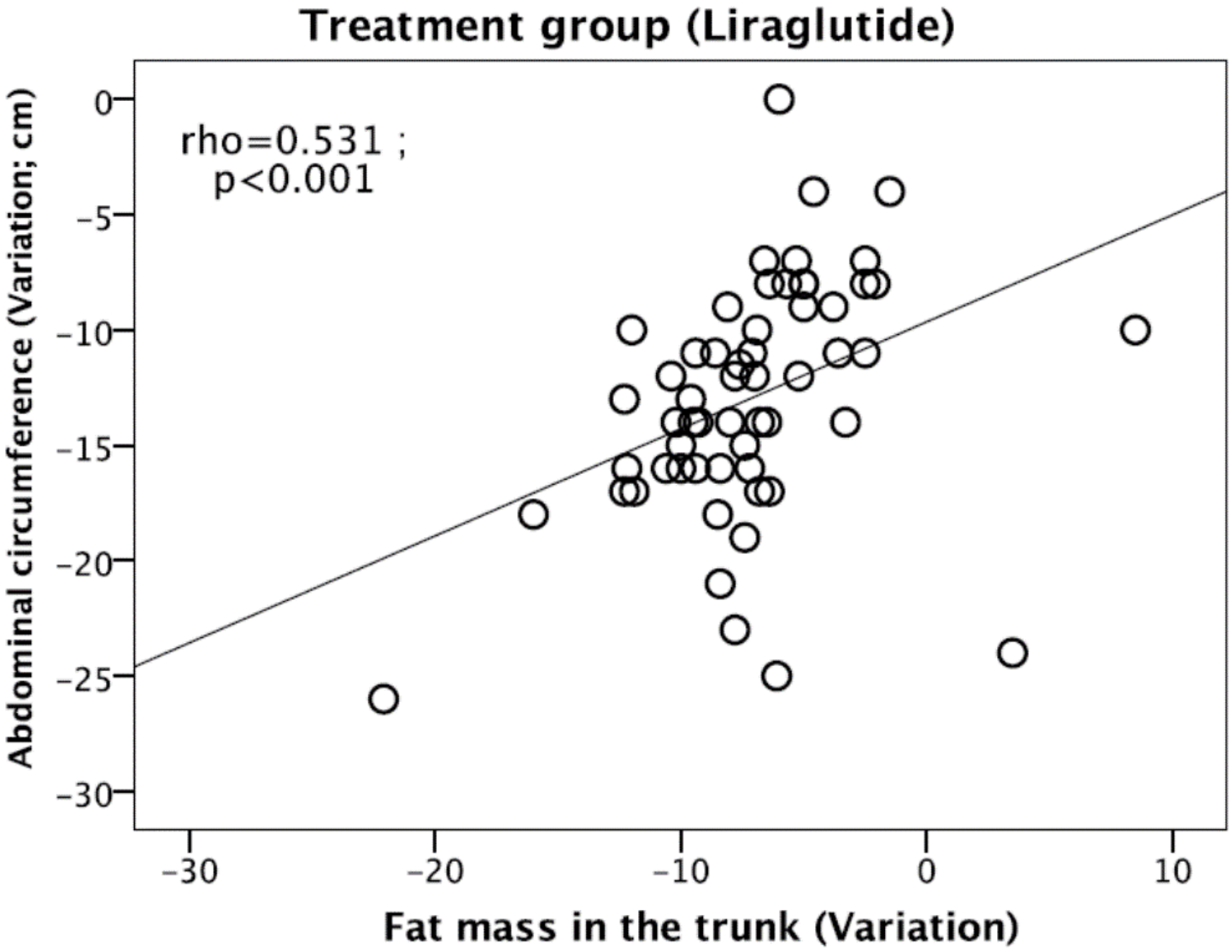

Figure 1

Correlation between reduction in abdominal circumference and reduction in fat mass in the trunk after 6 months of treatment with liraglutide.