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Relationship between adiponectin and muscle mass in patients with metabolic syndrome and obesity

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ABSTRACT

Background: Adiponectin is one of the most important adipokines in human beings. Obesity and sarcopenia are associated with a low-level chronic inflammatory status, and adiponectin plays an anti-inflammatory role.
Aims: The objective of the current work was to study the association between muscle mass, determined via bioelectrical impedance (BIA), and circulating adiponectin levels among obese patients with metabolic syndrome who are older than 60 years of age.
Methods: We performed a cross-sectional study incorporating 651 patients with obesity and metabolic syndrome. Anthropometric data, BIA data (total fat mass (FM), fat-free mass (FFM), fat-free mass index (FFMi), skeletal muscle mass (SMM) and skeletal muscle mass index (SMMi)), arterial pressure, HOMA-IR (homeostasis model assessment of insulin resistance), and biochemical parameters were recorded.
Results: The patients were separated into two groups based on their median SMMi (skeletal muscle mass index) levels. The low-SMMi group presented adiponectin levels that were higher than those in the high-SMMi group (delta value: 4.8 + 0.7 ng/dl: $p = 0.02$). Serum adiponectin values were negatively correlated with fat mass (FM), fat-free mass (FFM), fat-free mass index (FFMi), SMM, and SMMi. Adiponectin presented a negative correlation with HOMA-IR and a positive correlation with HDL-cholesterol. In the final multivariate model using SMMi as a dependent variable, adiponectin levels explained 18 % of the variability (Beta −0.49, CI95% −0.89 to −0.16) after adjusting for age and gender.
Conclusions: Serum adiponectin levels are negatively associated with low skeletal muscle mass among obese subjects with metabolic syndrome who are older than 60 years of age.

1. Introduction

Sarcopenia is a global skeletal muscle pathology that consists of the slow loss of skeletal muscle strength, muscle mass, and/or the ability to engage in physical activity.[1] This decrease in skeletal muscle function and mass may precipitate a reduced quality of life and increase the risk of falls, fractures, and mortality.[2] Additionally, some studies have revealed that sarcopenia is related to insulin resistance, metabolic syndrome (MS), and diabetes mellitus type 2.[3,4] Thus, a low-level chronic inflammatory status can be related to the etiology of sarcopenia and the malfunction of muscle tissue due to alterations, leading to an uncontrolled circuit of inflammation and muscle wasting.[4]

As mentioned above, body composition is related to metabolic health. Evaluating the body composition of subjects with obesity is difficult. It is important to use body composition parameters in order to achieve correct evaluations and diagnoses, especially in relation to the assessment of skeletal muscle mass and muscle function. In this situation, nutritional evaluations can no longer be performed based on the measurements used in classical anthropometric evaluations. The definition of a morphofunctional nutritional evaluation specifies that the corresponding nutritional evaluation must be realized using devices that measure anthropometric parameters and body composition, including devices used for bioelectrical impedance analysis, ultrasound, computerized axial tomography, magnetic resonance imaging, and other more sophisticated techniques.[5]

Taking into account all the previously mentioned information, there is only weak evidence available with which to determine the main roles of the endocrine system, fat mass, and inflammatory status in the evolution and onset of low muscle mass and activity. As is well known, adipose mass produces various bioactive molecules, which are

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collectively called adipokines. The unbalanced production and secretion of adipokines are correlated with chronic, low-grade inflammation, and this state is the main contributory factor in cardiovascular risk and MS. Adiponectin mediates an inflammatory status by modulating the production and secretion of IL6, IL8, and TNF-alpha and inhibiting the activation of NF-kappa Beta,[6] and this inflammatory status is related to MS.[3,4,6] Some investigations have reported that high levels of adiponectin provide a protective function against sarcopenia through binding to T-cadherin and stimulating muscle mass regeneration.[7] Additionally, there is a high rate of sarcopenia among patients with MS.[3,4,6] Moreover, previous investigations evaluating adiponectin serum levels in sarcopenic patients have shown conflicting results.[8] In their meta-analysis, Komici et al.[9] reported that subjects with sarcopenia presented significantly higher levels of adiponectin; this meta-analysis only evaluated patients with sarcopenia. Moreover, data obtained through human studies have shown that skeletal muscle also acts as an endocrine organ and secretes hormones (called myokines, in this case). Finally, greater fat mass significantly increases the risk of developing metabolic syndrome (MS).[10,11] MS constitutes a group of diseases related to obesity, including the impairment of glucose metabolism (intolerance or diabetes), central obesity, hyperlipidemia, and high blood pressure.[12] In this regard, another investigation reported that a higher fat-free mass was a protective factor against MS, perhaps secondary to an enhanced insulin sensitivity in skeletal muscle tissue.[13]

Thus, the main objective of this study was to analyze the association between muscle mass, determined via bioelectrical impedance as a morphofunctional nutritional assessment, and circulating adiponectin levels among obese subjects over 60 years old with metabolic syndrome. We sought to evaluate the crosstalk between molecules associated with adipose tissue (such as adiponectin), metabolic syndrome, and muscle mass in a risk population consisting of patients over 60 years old.

2. Patients and methods

2.1. Patients

This cross-sectional study was carried out from January 2022 to December 2022 in Valladolid, a Health Area located in the western of Castilla y Leon Community in Spain. The patients were selected using a consecutive non-probabilistic method. A total of 651 adults of both genders aged 60 years and older with obesity and metabolic syndrome were invited to participate in the study. All patients with obesity provided written informed consent, and the protocol employed complied with local institutional guidelines and the Declaration of Helsinki. The study protocol was validated by the local ethics committee (code registration: 06/2021).

The inclusion criteria for the current study were as follows: affliction with obesity (assessed as BMI $\geq$ 30 kg/m^2), an age above 60 years, and affliction with metabolic syndrome (MS). Subjects meeting 3 or more of the criteria shown in the following paragraph were classified as presenting metabolic syndrome (as defined using the Adult Treatment Panel III (ATPIII) criteria)[12]: elevated fasting glucose levels, high levels of triglycerides (>150 mg/dl) or drugs for hyperlipidemia, low levels of HDL cholesterol (specifically <40 mg/dl (males) or <50 mg/dl (females)), high arterial blood pressure levels (>130/85 mmHg or levels requiring the administration of antihypertensive drugs), and elevated waist circumference (>88 cm). The exclusion criteria were as follows: the presentation of any of the following conditions, namely, chronic kidney disease with a glomerular filtration rate <30 mL/min, chronic liver disease with a Child–Pugh grade of C, cardiac failure, tumors, and a recent history of alcoholism; the use of drugs that potentially influence body weight or related parameters (such as statins, fibrates, and treatments for diabetes mellitus); and the inability to walk/being bedridden.

The characteristics evaluated in the current study included socio-epidemiologic data, anthropometric parameters (height, body weight, calculated body mass index (BMI), and circumference of waist), bioimpedance parameters (total fat mass (FM), total fat-free mass (FFM), total fat-free mass index (FFMi), skeletal muscle mass (SMM) and skeletal muscle mass index (SMMi)), (systolic and diastolic) blood pressure, and biochemical parameters. During the basal visit, 10 ml of venous blood extracted following a 10-h overnight fast was obtained and poured into ethylenediaminetetraacetic acid EDTA-overcoated tubes. All the included patients were asked to collect data regarding their total dietary intake and physical activity.

2.2. Adiposity parameters, arterial blood pressure, and lifestyle parameters

Height, weight, and waist circumference were determined while the patients with obesity were fasting and wearing only light clothing. Waist circumference was determined to the nearest 0.1 cm. Waist circumference was measured just above the ilium using flexible plastic measuring tape (Omrom, Los Angeles, CA). Body height (in meters) was measured using a normal height scale (Omrom, Los Angeles, CA, USA), and body weight was determined using digital devices (Omrom, Los Angeles, CA, USA). BMI was determined using the following formula: body weight in kilograms divided by body height in meters squared.

Total fat mass and total fat-free mass were determined via bioelectrical impedance (BIA) analysis with a total accuracy of 50 g[14] (EFG BIA 101 Anniversary, Akern, It). The bioelectrical impedance analysis was performed in a standardized manner, with the patient fasting for 8 h and resting for 30 min. The electrodes were placed distally on the wrists and ankles of the patients, with the patients in a supine position and having assumed a lying position 30 min beforehand. Absolute fat-free mass (FFM) and skeletal muscle mass (SMM) were determined directly via impedance. Then, FFMi (fat-free mass index) was determined by dividing absolute FFM by squared height (FFM (kg)/height (m2)); SMMi (skeletal muscle mass index) was also determined by dividing SMM by squared height. Subjects were separated into 2 groups according to their median SMMi values.

Diastolic and systolic blood pressure were measured twice on each patient's dominant arm after a 10-min rest, and the average of the two measurements was determined using a sphygmomanometer (Omrom, LA, CA, USA).

All evaluated patients were instructed to save their daily dietary intake data for three non-consecutive days (two weekdays and one day on the weekend). Dietary records were obtained using specific software (Dietosource ®, Geneve, Swi), using national composition food tables as a reference [15]. The patients used a diary to record the minutes they spent performing physical activity every day.

2.3. Biochemical procedures and adiponectin

Serum biochemical determinations for fasting glucose levels, basal insulin levels, C-reactive protein (CRP) as an inflammatory marker, and lipid profiles were obtained using the COBAS INTEGRA 400 analyzer (Roche Diagnostic, Basel, Switzerland). Calculated LDL cholesterol was determined using the well-known Friedewald eq. (LDL cholesterol = total cholesterol − HDL cholesterol – triglycerides ÷ 5).[16] Taking into account the above-mentioned parameters, the homeostasis model assessment (HOMA-IR) was calculated (glucose (mml/L) × insulin (UI/L) / 22.5).[17] Adiponectin levels were determined using an enzyme-immunoassay method (ELISA) (R&D systems, Inc., Minnesota, USA). The normal range of adiponectin was 8.65–21.43 μg/ml.[18]

2.4. Statistical analysis

The Statistical Software for Social Sciences, version 23.0 (SPSS Statistics, IBM, Armonk, NY, USA), was employed to conduct analysis. Continuous variables are presented as means (standard deviation). Data normality of the variables was verified using the Kolmogorov–Smirnov test. After verifying that SMMi was a normal variable, we decided to

divide the sample into two groups according to the median of the SMMi. Frequency and absolute values were utilized for categorical parameters. The Student's *t*-test (for parametric parameters) or Mann–Whitney test (for non-parametric parameters) were used to compare the differences between continuous variables. Spearman or Pearson correlation evaluations were used to determine the relationship between the SSMi and biochemical parameters. Univariate and stepwise multivariate linear regressions were used to investigate the conditioning factors of SMMi. In the final multivariate model adjusted for age and gender, variables associated with SMMi in the univariate analysis ($p < 0.01$) were included. *P* values below 0.05 were considered statistically significant.

2.5. Ethical approval

All activities were in line with the ethical parameters of our local institutional research committee (HVUVA-committee 06/2021), and all the methods used were in line with the 1964 Declaration of Helsinki. Written informed consent was obtained from all the obese patients included in this cross-sectional study.

3. Results

A total of 651 patients with both entities (metabolic syndrome (MS) and obesity) were enrolled in this study, with an average age of 68.1 ± 5.3 years (range: 63–71). The adiposity parameters and biochemical characteristics of the population are shown in Table 1. As expected, total skeletal muscle mass (SMM) and relative muscle mass with respect to the skeletal muscle mass index (SMMi) were higher among males than among females.

Table 2 summarizes the dietary intake and physical exercise data of the whole group and the male and female groups. Total caloric intake and macronutrient distribution were similar in both the male and female groups.

Table 3 shows the patients divided into two different groups according to the median values of SMMi (13.42 kg/m^2), i.e., low SMMi vs high SMMi. Gender distribution and mean age were similar in both groups. As expected, BMI, weight, total fat-free mass (FFM), fat-free

Table 1
Basal parameters of both groups and in total (mean ± SD).

Parameters	Total group $n = 651$	Males $n = 338$	Females $n = 313$	P value
Age (years)	68.1 ± 5.3	68.3 ± 5.2	67.8 ± 5.1	0.28
BMI (kg/m 2)	39.5 ± 1.5	39.3 ± 1.7	39.6 ± 1.4	0.13
Weight (kg)	94.7 ± 2.1	95.3 ± 2.0	94.1 ± 1.9	0.29
Fat mass (kg)	44.4 ± 9.0	43.3 ± 9.1	45.3 ± 8.4	0.03
Fat-free mass (kg)	50.3 ± 8.9	50.2 ± 9.1	50.5 ± 8.1	0.39
Fat-free mass index (kg/m 2)	19.6 ± 2.6	19.4 ± 1.3	19.7 ± 2.7	0.41
Skeletal muscle mass (kg)	33.2 ± 6.1	35.4 ± 7.1	33.0 ± 9.4	0.02
Skeletal muscle mass index (kg/m2)	14.1 ± 5.1	14.4 ± 3.1	13.1 ± 4.9	0.02
WC (cm)	117.4 ± 12.1	116.1 ± 11.1	118.4 ± 12.3	0.12
SBP (mmHg)	136.3 ± 11.0	136.0 ± 9.0	136.5 ± 8.3	0.45
DBP (mmHg)	82.1 ± 8.1	81.4 ± 7.1	82.5 ± 8.0	0.41
Fasting Glucose (mg/dl)	112.9 ± 6.1	113.1 ± 5.1	112.7 ± 7.3	0.50
Total cholesterol (mg/dl)	203.2 ± 31.8	199.0 ± 39.8	207.1 ± 32.8	0.10
LDL-cholesterol (mg/dl)	121.7 ± 20.9	116.7 ± 18.9	128.7 ± 21.1	0.09
HDL-cholesterol (mg/dl)	54.9 ± 6.1	54.5 ± 4.1	55.5 ± 6.2	0.23
Triglycerides (mg/dl)	126.7 ± 20.0	126.3 ± 25.0	127.2 ± 18.0	0.31
Insulin (UI/l)	15.2 ± 2.2	15.7 ± 2.1	14.6 ± 2.0	0.21
HOMA-IR	4.2 ± 2.1	4.3 ± 1.1	4.2 ± 2.2	0.32
Adiponectin (ng/ml)	17.9 ± 0.8	14.1 ± 0.7	20.5 ± 0.9	0.01
CRP (mg/dl)	6.3 ± 2.3	6.2 ± 2.1	6.3 ± 2.4	0.23

BMI denotes body mass index; SBP denotes systolic blood pressure; DBP denotes diastolic blood pressure; HOMA-IR denotes homeostasis model assessment of insulin resistance; WC denotes waist circumference.

Table 2
Total average daily dietary intake and daily physical activity data (mean ± SD).

Parameters	Total group n = 651	Males n = 338	Females n = 313	P value
Calorie intake (kcal per day)	1806.1 ± 308.2	1882.1 ± 298.1	1800.1 ± 228.2	$p = 0.51$
Carbohydrate dietary intake (g per day) (PTC %)	200.8 ± 59.1 (46.1 %)	201.5 ± 60.1 (46.2 %)	199.5 ± 59.1 (46.0 %)	$p = 0.42$
Fat dietary intake (g per day) (PTC %)	72.6 ± 12.1 (33.5 %)	73.6 ± 13.2 (33.7 %)	70.9 ± 11.9 (33.6 %)	$p = 0.53$
Protein dietary intake (g/day) (PTC %)	100.8 ± 11.1 (20.4 %)	99.3 ± 13.0 (20.1 %)	101.5 ± 9.0 (20.4 %)	$p = 0.32$
Fiber dietary intake (g per day)	16.5 ± 6.0	16.1 ± 5.1	16.8 ± 4.9	$p = 0.29$
Total Physical activity (min per week)	128.1 ± 12.2	129.3 ± 9.8	127.3 ± 13.1	$p = 0.46$

PTC: Percentage of total calories. Last column: no statistical differences.

Table 3
Basal parameters of both groups and in total (mean ± SD).

Parameters	Total group n = 651	Low-SMMi $n = 325$	High-SMMi $n = 326$	P value
Gender (male/female)%	330/321 (50.7/49.3 %)	166/159 (51.1/49.9 %)	164/162 (50.8/49.2 %)	0.37
Age (years)	68.1 ± 5.3	68.4 ± 5.1	67.7 ± 5.4	0.29
BMI (kg/m 2)	39.5 ± 1.5	38.3 ± 1.6	39.9 ± 1.2	0.03
Weight (kg)	94.7 ± 2.1	88.8 ± 2.0	96.2 ± 4.9	0.04
Fat mass (kg)	44.4 ± 9.0	44.2 ± 7.1	44.7 ± 8.1	0.43
Fat-free mass (kg)	50.3 ± 8.9	45.5 ± 8.1	55.2 ± 8.8	0.01
Fat-free mass index (kg/m 2)	19.6 ± 2.6	18.8 ± 1.9	23.3 ± 2.8	0.02
Skeletal muscle mass (kg)	33.2 ± 6.1	29.2 ± 3.1	39.9 ± 7.4	0.01
Skeletal muscle mass index (kg/m2)	14.1 ± 5.1	11.9 ± 3.2	16.2 ± 4.9	0.02
WC (cm)	117.4 ± 12.1	113.1 ± 11.1	121.1 ± 12.3	0.03
SBP (mmHg)	136.3 ± 11.0	134.0 ± 9.0	137.5 ± 11.3	0.45
DBP (mmHg)	82.1 ± 8.1	81.2 ± 4.1	82.6 ± 8.1	0.41
Fasting Glucose (mg/dl)	112.9 ± 6.1	110.1 ± 5.2	111.9 ± 5.3	0.40
Total-cholesterol (mg/dl)	203.2 ± 31.8	204.0 ± 30.8	201.5 ± 32.9	0.14
LDL-cholesterol (mg/dl)	121.7 ± 20.9	123.7 ± 18.1	120.5 ± 21.2	0.39
HDL-cholesterol (mg/dl)	54.9 ± 6.1	56.5 ± 4.1	54.5 ± 4.2	0.23
Triglycerides (mg/dl)	126.7 ± 20.0	122.3 ± 21.1	127.9 ± 19.9	0.31
Insulin (UI/l)	15.2 ± 2.2	13.6 ± 2.1	16.3 ± 2.2	0.29
HOMA-IR	4.2 ± 2.1	3.6 ± 1.2	4.6 ± 2.2	0.32
Adiponectin (ng/ml)	17.9 ± 0.8	20.9 ± 0.5	16.1 ± 0.9	0.01
C Reactive protein (mg/dl)	6.3 ± 2.3	5.9 ± 2.1	6.4 ± 2.7	0.27

BMI denotes body mass index; DBP denotes diastolic-blood pressure; HOMA-IR denotes homeostasis model assessment; SBP denotes systolic blood pressure; WC denotes waist circumference.

mass index (FFMi), SMM, and SMMi were higher in the high-SMMi group than in the low-SMMi group. Adiponectin serum levels were higher in the low-SMMi group than in the high-SMMi group (delta value: 4.8 ± 0.7 ng/dl: $p = 0.02$).

Table 4 shows the caloric intake and physical exercise data of the whole cohort and those of the male and female groups. Total energy intake and macronutrient percentages were similar in both groups.

Table 5 presents the correlation analysis of the adiponectin, insulin, and HOMA-IR values with respect to the patients' anthropometric parameters and biochemical data. Serum adiponectin levels were negatively correlated with total fat mass (FM), total fat-free mass (FFM), fat-free mass index (FFMi), SMM, and SMMi. Adiponectin values presented a negative association with HOMA-IR and a positive association with HDL-cholesterol. Fasting insulin levels and HOMA-IR showed a positive correlation with weight, waist circumference, FM, FFM, FFMi, SMM, and SMMi. HOMA-IR and insulin showed a positive correlation with triglycerides and C-reactive protein. Both values showed a negative correlation with the measured HDL-cholesterol levels.

CRP denotes C-reactive protein. HOMA-IR denotes homeostasis model assessment of insulin resistance.

Stepwise multivariate linear regression adjusted for potential confounder factors such as weight, waist circumference, physical activity, age, and gender was used to investigate the conditions of SMMi. In the multivariate model adjusted for age and sex, protein intake and parameters related to SMMi in the final univariate analysis ($p < 0.01$) were used. Insulin levels and serum adiponectin levels were retained in both models. In the final model using SMMi as a dependent variable, serum adiponectin levels represented 18 % of the variability (Beta −0.49, CI95% −0.89 to −0.16), and insulin values represented 21 % of the variability (Beta 0.53, CI95% 0.23–4.12).

Table 4
Daily dietary intake and physical exercise data (mean ± SD).

Parameters	Total group n = 651	Low SMMI n = 325	High SMMI n = 326	P value
Calorie intake (kcal/day)	1886.1 ± 308.2	1844.9 ± 212.1	1893.1 ± 218.9	$p = 0.53$
Carbohydrate dietary intake (g/day) (PTC %)	200.8 ± 59.1 (46.1 %)	201.5 ± 61.1 (46.4 %)	199.9 ± 58.1 (46.0 %)	$p = 0.49$
Fat dietary intake (g/day) (PTC%)	72.6 ± 12.1 (33.5 %)	73.6 ± 12.2 (33.4 %)	71.1 ± 10.9 (33.3 %)	$p = 0.54$
Protein dietary intake (g/day) (PTC%)	98.8 ± 11.1 (20.4 %)	99.6 ± 12.0 (20.2 %)	97.5 ± 9.1 (20.7 %)	$p = 0.39$
Fiber dietary intake (g/day)	16.5 ± 6.0	16.9 ± 5.0	16.1 ± 5.9	$p = 0.21$
Total physical activity (min/week)	128.1 ± 12.2	125.3 ± 9.1	129.1 ± 10.2	$p = 0.46$

PTC: Percentage of total calories. Last column: p values.

Table 5
Correlation evaluation between adiponectin levels, impedance bioelectrical, and biochemical parameters.

Parameters ultrasound	Adiponectin	Insulin	HOMA-IR
BMI (kg/m^2)	$r = -0.017$, $p = 0.31$	$r = 0.048$, $p = 0.39$	$r = 0.058$, $p = 0.59$
Weight (kg)	$r = -0.161$, $p = 0.061$	*$r = 0.381$, $p = 0.001$*	*$r = 0.299$, $p = 0.001$*
Waist Circumference (cm)	$r = -0.148$, $p = 0.12$	*$r = 0.305$, $p = 0.002$*	*$r = 0.329$, $p = 0.003$*
Fat mass (kg)	$r = -0.27$, $p = 0.03$	*$r = 0.168$, $p = 0.005$*	*$r = 0.150$, $p = 0.012$*
Fat-free mass (kg)	*$r = -0.34$, $p = 0.005$*	*$r = 0.154$,$p = 0.008$*	*$r = 0.156$, $p = 0.009$*
Fat-free mass index (kg/m^2)	*$r = -0.25$, $p = 0.007$*	*$r = 0.135$, $p = 0.02$*	*$r = 0.132$, $p = 0.02$*
Skeletal muscle mass (kg)	*$r = -0.37$, $p = 0.001$*	*$r = 0.149$, $p = 0.011$*	*$r = 0.145$, $p = 0.012$*
Skeletal muscle mass index (kg/m^2)	*$r = -0.21$, $p = 0.021$*	*$r = 0.136$, $p = 0.021$*	*$r = 0.130$, $p = 0.01$*
Insulin (UI/L)	$r = -0.03$, p = 0.59	–	–
HOMA-IR	$r = -0.24$, p = 0.01	–	–
CRP (mg/dl)	$r = -0.05$, $p = 0.24$	$r = 0.12$, $p = 0.05$	*$r = 0.13$, $p = 0.04$*
LDL-Cholesterol (mg/dL)	$r = -0.04$, $p = 0.45$	$r = -0.06$, $p = 0.43$	$r = -0.09$, p = 0.42
HDL-Cholesterol (mg/dl)	*$r = 0.33$, $p = 0.01$*	*$r = -0.25$, $p = 0.01$*	*$r = -0.26$, $p = 0.01$*
Triglycerides (mg/dl)	$r = -0.10$, p = 0.39	*$r = 0.26$, $p = 0.02$*	*$r = 0.31$, $p = 0.01$*
Adiponectin (ng/ml)	–	r = −0.03, p = 0.59	$r = -0.24$, p = 0.01

4. Discussion

To the best of our knowledge, our study is the first clinical investigation to determine the potential relationship between skeletal muscle mass determined via bioelectrical impedance analysis (BIA) and serum values of adiponectin among patients with obesity and metabolic syndrome (MS). In our study, serum levels of adiponectin were elevated in the low-skeletal-muscle-mass-index (SMMi) group and demonstrated a significative inverse correlation with fat mass (FM), fat-free mass index (FFMi), fat-free mass (FFM), and SMMi and a positive correlation with HDL-cholesterol.

Adiponectin has anti-inflammatory, antidiabetic, and anti-atherogenic properties.[19] This molecule is present in higher levels in females than in males[20] (data found in our study). This molecule exhibits a lot of properties, such as enhancing glucose intake by the cells and preventing gluconeogenesis and fatty acid storage by activating different pathways.[21] It is synthesized and released by adipose mass and skeletal muscle, affects total muscle mass and the liver, and regulates inflammatory processes by preventing the production of proinflammatory markers.[21] Patients with obesity usually present low levels of adiponectin. In these patients, adiponectin is related to body weight, waist circumference, body mass index, inflammatory status, cardiovascular risk, and impaired insulin signaling.[21] In the literature, according to a recent meta-analysis recruiting 557 subjects with sarcopenia, subjects with low muscle mass are more likely to show higher serum values of adiponectin.[9] Elevated adiponectin serum levels in subjects with sarcopenia are still being reported.[4,9,19,22] Some plausible postulates have been proposed to explain the described association, namely, the accumulation of adipose tissue in muscle mass, which may modulate adiponectin expression[22]; the downregulation of adiponectin receptor signaling[23]; and the enhancement of muscle catabolism due to the coexistence of other important entities.[21] Accordingly, in our investigation, serum levels of adiponectin were significantly elevated in the low-SMMi subgroup and negatively correlated with muscle mass among the subjects with obesity and MS.

The novelty of our study is that the previously mentioned studies were conducted on patients with sarcopenia, while our work evaluates the relationship between serum levels of adiponectin in a group of patients with obesity and MS. The relationship between sarcopenia and chronic inflammation may be modulated by total adipose tissue, which could also induce sarcopenic obesity.[10,24] In the literature, studies have focused on elderly and non-obese patients; however, they have found the same inverse relationship between circulating adiponectin levels and muscle mass,[24,25] which, in this study, was determined via densitometry and without taking into account insulin or HOMA-IR. Lower levels of adiponectin have been reported in older adults with sarcopenia versus older adults without sarcopenia. Moreover, there have been epidemiological studies that reported associations between different muscle parameters, such as low muscle mass circumference, poor function, low muscle eco-intensity, and low strength, and a high incidence of sarcopenia.[26,27] Perhaps some of the discrepancies in the data from the previous studies, which did not present statistical differences in serum

adiponectin levels between different groups of patients with different muscle mass parameters,[9] could be explained by confounding factors that were unaccounted for. Firstly, the presence of the peripheral resistance of the tissues to the action of adiponectin and, secondly, the lack of the correction of the results according to the age of the population, considering that circulating adiponectin levels rise with age, may relate to the confounding action of peripheral adiponectin resistance and the elevation of serum adiponectin levels with aging in these populations.[9] Some authors have called this phenomenon the "adiponectin paradox", as the reason behind its occurrence is unclear. It is possible that "normal" or "healthy" ranges of circulating serum adiponectin may present as a U-shaped risk curve during a follow-up occurring when a patient has aged further. The functional consequences of this fact are a decrease in adiponectin sequestration by responsive tissues, an increase in adiponectin levels in circulation, and a secondary decrease in signal transduction. This process creates the paradoxical situation wherein adiponectin levels are increased, whereas adiponectin signal transduction and insulin sensitivity remain decreased.

The most plausible hypothesis with which to explain all the above-mentioned associations is the inflammatory hypothesis. Our current observations are in agreement with the findings of the above-mentioned article,[9] which contends that low muscle mass and the related catabolic status constitute the pathophysiological background leading to the upregulation of adiponectin levels as part of counterbalance mechanisms against chronic inflammatory status in these patients.[28] For example, the upregulation of total adiponectin expression in the muscles of diabetic and obese mice has been reported.[29] On the other hand, insulin resistance and elevated CRP levels have also been described in subjects with low muscle mass.[30] Another hypothesis postulates the involvement of an elevated serum adiponectin concentration as a well-known compensatory mechanism counteracting low muscle mass, as reported in the regrowth of unloading-related atrophied muscle,[31] which might increase protein synthesis via the PI3K-Akt pathway.[32] Perhaps the expression of specific adipokine receptors in skeletal muscle is a key determinant in all these processes and a main actor in the progression of sarcopenia in these patients. In this way, adiponectin receptor 1 (AdipoR1) is the main form produced in skeletal muscle mass and appears to be downregulated in patients with diabetes mellitus type 2, obesity, metabolic syndrome, and/or chronic heart failure.[33] This downregulation of the expression of AdipoR1 likely negatively influences the sensitivity of the skeletal muscle to serum circulating levels of adiponectin, thereby inducing insulin resistance and, consequently, possibly contributing to sarcopenia. Moreover, in our study, the levels of circulating insulin were also related to muscle mass, probably in relation to the anabolizing activity of this hormone.[34]

Additionally, an association between serum adiponectin levels and lipid profiles has been previously reported.[35,36] Elevated levels of circulating adiponectin are related to a better lipid profile. Serum adiponectin levels are positively associated with measured HDL-cholesterol and negatively associated with triglycerides and LDL cholesterol, indicating a key role in dyslipidemia and secondary cardiovascular risk.[35] One study[36] has reported that circulating HDL-cholesterol increases the gene expression of adiponectin through the Ca2+/calmodulin (CaM)-dependent protein kinase IV (CaMKIV) pathway.[39]

Finally, the use of body composition determinations is essential for accurate assessment, especially for the evaluation of subjects with obesity and MS. Bioelectrical impedance analysis, a morphofunctional nutritional method, is a well-known technique, and the electrical parameters used therein serve as direct measurements, allowing us to determine accurate values of fat mass and fat-free mass.[38] Skeletal muscle mass contains the largest volume of cell mass in the body, and it holds a high-water concentration, which is a good electric conductor. The direct relationship between the electrical parameters of bioelectrical impedance analysis and muscle mass and fat-free mass has been described previously.[38] The increase in muscle cells leads to an increase in cell membrane coverage and, therefore, in reactance and other electrical parameters such as phase angle. The use of BIA has been shown to be useful as a non-invasive and portable technique for the evaluation of these patients in the context of a morphofunctional assessment (as presented in our study).

The present study has several limitations and strengths. The limitations of our study are as follows: Firstly, our study only incorporated Caucasian subjects with obesity and metabolic syndrome, so the obtained data cannot be extrapolated to other ethnicities or races, children, overweight subjects, or other patients with obesity and without MS. Secondly, this investigation's cross-sectional design precludes the inference of causality. Thirdly, our study was likely influenced by selection bias because it was based on a single hospital. Fourthly, dietary intake was based on self-reports obtained from patients with a potential bias. Fifthly, while a wide range of techniques can be used to assess muscle mass, we used bioelectrical impedance, which could precipitate potential bias.[39] BIA, especially non-segmental BIA, cannot be used to measure skeletal muscle mass. The BIA performed in this study was used to extract data on fat and fat-free mass. Skeletal muscle mass was estimated from the fat-free mass using various algorithms. Finally, in our study, we have not determined muscle strength or functionality. Some strengths of our study are the control of nutritional intake as a possible confounding factor, in addition to physical activity, and that the representation of both genders was similar.

5. Conclusions

In conclusion, serum adiponectin levels are related to low skeletal muscle mass among subjects with obesity who are ≥60 years old and afflicted with metabolic syndrome. Considering the evidence of adiponectin's regenerative and anti-inflammatory role, our results indicate that it is an important potential marker associated with muscle damage brought about by low SMMi values, thus prompting the need for more studies in the areas of therapy and diagnosis. Our investigation is a pioneering study whose results require further investigation using other technologies and populations, questionnaires to confirm robustness of the results, and an evaluation of the implications in clinical settings to achieve a better understanding of the association between adipose tissue via analyzing adiponectin and skeletal muscle mass among patients potentially at risk of developing sarcopenia and afflicted with metabolic syndrome.[37]

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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of our Hospital.

Informed consent statement

Informed consent was recorded from all subjects involved in the study.

CRediT authorship contribution statement

Daniel de Luis: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **David Primo:** Investigation, Methodology. **Olatz Izaola:** Investigation, Methodology. **Juan José Lopez Gomez:** Formal analysis, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: Daniel de Luis reports was provided by University of Valladolid. Daniel de LUis reports a relationship with University of Valladolid that includes: board membership.

Data availability

All of the present data that support the results of this study are available from the corresponding author upon reasonable request.

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