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Relationship between fat-free mass and metabolic syndrome in obese females

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Abstract. – OBJECTIVE: A greater fat-free mass (FFM) could be negatively or positively associated with metabolic syndrome (MS). The objective of this work was to evaluate the relationship of FFM with MS, through three determinations; absolute FFM, relative to body weight FFM% and relative to squared height (FFMi).

PATIENTS AND METHODS: We conducted a cross-sectional study on 1,008 obese Caucasian females. Fat-free mass index (FFMi) was calculated by dividing FFM by squared height [FFM (kg)/height (m^2)]. Fat-free mass percentage (FFM%) was calculated (absolute FFM/body weight) x100.

RESULTS: The odds ratio adjusted by age of having MS per tertiles were significantly higher in tertile 3 of FFM (OR=1.74, 95% CI=1.26-2.41; *p*=0.01) and FFMi (OR=3.38, 95% CI=2.42-3.72; *p*=0.001) and tertile 2 of FFM (OR=1.45, 95% CI=1.08-1.94; *p*=0.02) and FFMi (OR=2.37, 95% CI=1.75-3.20; *p*=0.01) compared with its reference (tertile-1). In contrast, odds ratio adjusted by age of having MS per tertiles were significantly lower in tertile-3 of FFM% (OR=0.29, 95% CI=0.20-0.41; *p*=0.01) and tertile- 2 of FFM% (OR=0.68, 95% CI=0.51-0.91; *p*=0.01) compared with its reference (tertile-1).

CONCLUSIONS: The prevalence of MS relative to FFM varies depending on the method used to represent it.

Key Words:

Fat-free mass, Fat-free mass index, Fat-free mass percentage, Females, Metabolic syndrome, Obesity.

Introduction

Body composition is related with metabolic health. Adipose tissue is an important endocrine organ that synthetizes proteins with many biological roles, including adipokines[1]. Greater fat mass (FM) significantly increases the risk of having the metabolic syndrome (MS) and diabetes mellitus type 2[2,3]. Additionally, some studies[4,5] have detected that sarcopenia, a state of reduced fat-free mass (FFM), is associated with insulin resistance and diabetes mellitus type 2. Thus, a greater baseline FMM, relative to total body weight, was associated with a better metabolic health[6]. In this regard, another investigation[7] reported that a higher FFM percentage, relative to body weight again, was a protective factor against metabolic syndrome. This positive relationship between a large FFM and a good metabolic health is rationalized by two physiological mechanisms. First, a greater FFM may protect subjects from adipose accumulation through greater resting energy expenditure[8], this is secondary to the bioactive nature of FFM. Second, FFM has a large proportion of glucose uptake under insulin-stimulated conditions[9], in this way a larger FFM regulates glucose homeostasis[10].

Moreover, based on other investigations[11-16] and in contrast with the above-mentioned hypothesis, they have been reported that a greater FFM could be negatively associated with metabolic syndrome and insulin resistance. These conflicting results could be explained from the different ways FFM is measured in these investigations. Representing FFM in different ways (relative to height or relative to weight) leads to different conclusions taking to account the association with metabolic syndrome and insulin resistance[4,5,17]. For example, odds ratio of MS was significantly reduced when FFM was evaluated as relative to body weight[4]. In contrast, representing FFM relative to squared height (m^2) led to greater FFM being associated with higher odds ratio of MS[4]. Finally, Bijlsma et al[5] reported a deleterious relation of greater appendicular FFM on insulin resistance.

Metabolic syndrome (MS) is a constellation of risk entities related with obesity, including glucose intolerance or diabetes mellitus, abdominal obesity, hyperlipidemia, and high blood pressure levels[18]. MS is considered a polygenic and multifactorial disorder due to the interaction of numerous genes with environmental factors; in this context, body composition develops an important role in the

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presence of MS[19]. Nowadays, MS is an important health problem in females[20]. Consequently, additional studies are needed to evaluate the role of FFM in females and the association of this parameter on the presence on metabolic syndrome.

The objective of this work was to evaluate the relationship of FFM with MS, through three determinations; absolute FFM, relative to body weight FFM% and relative to squared height (FFMi) on Caucasian females with obesity.

Patients and Methods

Subjects

This study was a cross-sectional design including adult Caucasian Obese females (20 to 79 years) in a Health Area of Castilla y Leon Community in Spain. Consecutive voluntary females with body mass index (BMI) >30 kg/m^2 were included (1,008 study subjects). All participants provided written informed consent, and the protocol complies with the Declaration of Helsinki as well as with local institutional guidelines. It was approved by the Ethics Committee (code of registration 06/2021).

The inclusion criterion for the protocol were obesity assessed as body mass index >30 kg/m^2 and an age in the range 20-79 years. Exclusion criteria were the presence of any associated condition (e.g., chronic kidney disease, chronic liver disease, heart failure, uncontrolled hypothyroidism, Cushing's disease, malignant tumors and history of alcoholism) or use of medications that potentially influenced weight or metabolic parameters (statins, fibrates and drugs against diabetes mellitus).

The variables of the present study included sociodemographic data, classical anthropometric parameters [weight, height, body mass index (BMI) and waist circumference), anthropometric parameters by bioimpedance (total fat mass (FM), fat-free mass (FFM), fat-free mass percentage (FFM%), fat-free mass index (FFMi)], blood pressure and biochemical assessment. During the recruitment visit, 20 ml of venous blood after an 8 hour overnight fast were aliquoted in ethylenediaminetetraacetic acid EDTA-coated tubes for biochemical analysis.

Anthropometric Parameters and Blood Pressure

Height, weight, and waist circumference were measured in the morning while the subjects were fasting and wearing only light clothing without shoes. Waist circumference was measured at the nearest 0.1 cm just above the ilium with a flexible standard tape (Omrom, Los Angeles, CA, USA). Body height (cm) was determined using a standard height measurement scale (Omrom, Los Angeles, CA, USA) and body weight was measured using digital scales (Omrom, Los Angeles, CA, USA). Body mass index (BMI) was calculated with the following equation: weight in kilograms divided by height in squared meters.

Total fat mass and fat-free mass was obtained by impedance with an accuracy of 50 g[21] (EFG BIA 101 Anniversary, Akern, Pisa, Italy). Absolute fat-free mass (FFM) was calculated directly by impedance. Then, FFMi was calculated by dividing absolute FFM by squared height [FFM (kg)/height (m^2)]. Fat-free mass percentage (FFM%) was calculated using the following equation: (absolute FFM/body weight)x100. The tertiles of these parameters were determined.

Systolic and diastolic blood pressures were measured three consecutive times on the right arm after 10 minutes rest, and average of the three measures was calculated with a sphygmomanometer (Omrom, LA, CA, USA).

Metabolic Syndrome

Females with three or more of the components listed in the text were considered as having the metabolic syndrome (MS), as defined using the Adult Treatment Panel III (ATPIII) criteria[18]. The ATPIII definition recognizes the following cut-offs for defining MS: elevated fasting glucose or treatment for diabetes mellitus, elevated triglycerides (>150 mg/dl) or treatment for hyperlipidemia, high density lipoprotein (HDL) cholesterol <40 mg/dl (males) or <50 mg/dl (females), elevated systolic or diastolic blood pressure (>130/85 mmHg) or antihypertensive treatment) and increased waist circumference (>88 cm).

Biochemical Procedures

Serum biochemistry analysis for glucose, insulin, C reactive protein CRP, total cholesterol, HDL-cholesterol, triglyceride, and interleukine-6 were realized using the COBAS INTEGRA 400 analyzer (Roche Diagnostic, Basel, Switzerland). LDL cholesterol was calculated using Friedewald equation (LDL cholesterol=total cholesterol-HDL cholesterol-triglycerides/5)[22]. Based on these parameters, homeostasis model assessment for insulin resistance (HOMA-IR) was obtained using these values [glucose (mml/L) x insulin (UI/L)/22.5][23]. IL-6 was measured by enzyme immunoassay (ELISA) (Biovendor Laboratory, Inc., Brno, Czech Republic).

Statistical Analysis

Continuous data are presented as mean±standard deviation. The normality of the variables was tested using the Kolmogorov-Smirnov test. Percentage and absolute values were used for categorical parameters. Continuous variables were analyzed with Student *t*-test (for normally distributed variable) or Mann-Whitney U test (for non-normally distributed variable). Differences in MS prevalence between tertiles of FFM, FFMi and FMM% were assessed with Chi-square test. The odds ratio (OR) was determined with a 95% confidence interval to assess the influence of this indexes (FFM, FFMi and FMM%) on the presence of metabolic syndrome and its components. *p*-values below 0.05 were considered statistically significant. Statistical analysis was performed using SPSS v. 23 software (IBM Corp., Armonk, NY, USA).

Results

1,008 Caucasian females obese were enrolled with an average age of 49.9±15.3 years (range: 27-79). 413 subjects had MS (41.0%) and 595 did not show MS (59.0%). The anthropometric and biochemical characteristics of the population are showed in Table I.

Table I. Basal parameters in total group (Mean±SD).

Parameters	Total Group n=1,008
Age (years)	49.9±15.3
BMI (kg/m^2)	36.9±1.5
Weight (kg)	94.4± 5.1
Fat mass (kg)	41.7± 9.1
Fat-free mass (kg)	50.6±11.9
Fat-free mass index (kg/m^2)	19.6± 3.6
Fat-free mass % (kg)	54.46±10.1
WC (cm)	111.4±14.1
SBP (mmHg)	128.4±16.0
DBP (mmHg)	81.5±10.1
Fasting Glucose (mg/dl)	101.9± 9.1
Total cholesterol (mg/dl)	202.2±30.8
LDL-cholesterol (mg/dl)	123.9±30.9
HDL-cholesterol (mg/dl)	54.1±14.1
Triglycerides (mg/dl)	121.2±50.0
Insulin (mUI/l)	14.7±1.2
CRP (mg/dl)	6.1±2.3
IL6 (PG/MO)	2.4±0.8

BMI: body mass index DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference.

Table II summarizes the anthropometric parameters and blood pressure levels. A greater level of body mass index, weight fat mass, waist circumference and fat mass were observed with increasing tertiles of fat-free mass (FFM) and fat-free mass index (FFMi). In contrast, these above-mentioned levels decreased with greater tertiles of fat-free mass relative to body weight (FFM%). Similar results were observed with systolic and diastolic blood pressure levels.

Table III shows lipid profile, glucose metabolism parameters and inflammatory markers. A greater level of glucose, triglycerides, C reactive protein, insulin, HOMA-IR and interleukin-6 was detected in tertile 3 of FFM and FFMi compared with tertiles 2 and 1. Unlike, a greater level of the same parameters was detected in tertile 1 of FFM% compared with tertiles 2 and 3. HDL-cholesterol was lower in tertile 3 of FFM and FFMi compared with tertiles 2 and 1. In contrast, HDL-cholesterol was higher in tertile 1 of FFM% compared with tertiles 2 and 3. Total cholesterol and LDL-cholesterol remained unchanged throughout different tertiles with the three indexes.

Table IV summarizes the percentage of MS and its components in different tertiles. A greater prevalence of MS was detected with increasing tertiles of FFM and FFMi. In contrast, prevalence of MS decreased with greater tertiles of FFM%. The odds ratio adjusted by age of having MS per tertiles were significantly higher in tertile 3 of FFM (OR=1.74, 95% CI=1.26-2.41; p=0.01) and FFMi (OR=3.38, 95% CI=2.42-3.72; p=0.001) and tertile 2 of FFM (OR=1.45, 95% CI=1.08-1.94; p=0.02) and FFMi (OR=2.37, 95% CI=1.75-3.20; p=0.01) compared with its reference (tertile 1). In contrast, odds ratio adjusted by age of having MS per tertiles were significantly lower in tertile 3 of FFM% (OR=0.29, 95% CI=0.20-0.41; p=0.01) and tertile 2 of FFM% (OR=0.68, 95% CI=0.51-0.91; p=0.01) compared with its reference (tertile 1).

Given the modified odds ratio of having the MS with FFM, FFMi, and FFM%, we verified if the specific component of the MS was driving these results (Table V). The odds ratio of having an elevated waist circumference, hypertriglyceridemia percentage, low HDL-cholesterol levels percentage, hypertension or hyperglycemia were significantly greater in almost every tertile of FFM and FFMi compares tertile 1. Finally, the odds ratio of having an elevated waist circumference, hypertriglyceridemia percentage, low HDL-cholesterol levels percentage, hypertension or hyperglycemia were significantly lower in almost every tertile of FFM% compares tertile 1 (Table V).

Table II. Anthropometric parameters and blood pressure by tertiles (FFM, FFMi, FFM%) (mean ± SD).

Parameters	Total fat-free mass				Fat-free mass index				Fat-free mass percentage			
	Tertile 1	Tertile 2	Tertile 3	*p*	Tertile 1	Tertile 2	Tertile 3	*p*	Tertile 1	Tertile 2	Tertile 3	*p*
BMI (kg/m^2)	34.7±1.3	35.8±1.1$^{\#}$	39.9±1.0$^{*,\$}$	0.01	33.9±3.2	36.3±1.2$^{\#}$	41.1±1.1$^{*,\$}$	0.02	40.2±1.2	35.6±1.4$^{\#}$	33.4±1.7$^{*,\$}$	0.001
Weight (kg)	81.7±2.1	90.9±2.0$^{\#}$	108.7±3.3$^{*,\$}$	0.01	84.2±2.9	91.4±3.2$^{\#}$	107.7±2.9$^{*,\$}$	0.02	99.1±2.3	90.8±2.1$^{\#}$	87.5±2.3$^{*,\$}$	0.01
Fat mass (kg)	37.1±2.3	41.3±2.5$^{\#}$	45.2±2.2$^{*,\$}$	0.02	39.0±0.6	41.2±1.1$^{\#}$	44.8±0.9$^{*,\$}$	0.01	53.2±2.1	40.2±2.0$^{\#}$	32.2±2.1$^{*,\$}$	0.01
Fat-free mass (kg)	39.9±5.6	48.6±4.1$^{\#}$	63.1±7.0$^{*,\$}$	0.01	42.1±5.1	49.3±4.0$^{\#}$	62.5±5.1$^{*,\$}$	0.01	45.9±4.1	50.6±3.1$^{\#}$	57.8±4.0$^{*,\$}$	0.01
Fat-free mass index (kg/m^2)	14.7±2.3	19.2±1.5$^{\#}$	23.1±2.0$^{*,\$}$	0.02	16.0±2.1	19.6±1.4$^{\#}$	23.2±1.0$^{*,\$}$	0.02	15.1±1.3	19.7±1.0$^{\#}$	22.1±2.1$^{*,\$}$	0.02
Fat-free mass % (kg/kgx100)	50.2±6.3	54.4±4.5$^{\#}$	58.7±5.2$^{*,\$}$	0.01	51.0±3.3	54.9±2.5$^{\#}$	58.6±3.2$^{*,\$}$	0.01	46.1±6.0	55.4±4.1$^{\#}$	64.6±5.0$^{*,\$}$	0.02
WC (cm)	103.4±9.1	108.9±7.3$^{\#}$	120.6±8.1$^{*,\$}$	0.01	103.3±3.1	110.9±3.2$^{\#}$	121.4±2.1$^{*,\$}$	0.02	115.4±7.1	109.9±6.2$^{\#}$	107.2±4.1*	0.03
SBP (mmHg)	125.1±9.2	126.7±8.2	131.9±7.0$^{*,\$}$	0.03	124.1±6.1	125.3±2.1	132.1±4.0$^{*,\$}$	0.04	132.1±4.2	127.1±4.3$^{\#}$	126.2±4.0*	0.03
DBP (mmHg)	79.4±2.1	81.3±3.0	84.2±2.0$^{*,\$}$	0.03	78.9±2.0	80.2±2.1	86.4±1.1$^{*,\$}$	0.03	83.7±2.0	79.3±3.1$^{\#}$	80.2±1.9*	0.03

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference. *p*-values ANOVA Snedecor-F test. Post-hoc Bonferroni test. *Statistical differences between tertile 3 and tertile 1. $^{\$}$ Statistical differences between tertile 3 and tertile 2. $^{\#}$Statistical differences between tertile 2 and tertile 1.

Table III. Biochemical parameters by tertiles (FFM, FFMi, FFM%) (mean±SD).

Parameters	Total fat-free mass				Fat-free mass index				Fat-free mass percentage			
	Tertile 1	Tertile 2	Tertile 3	*p*	Tertile 1	Tertile 2	Tertile 3	*p*	Tertile 1	Tertile 2	Tertile 3	*p*
Glucose (mg/dl)	100.5±4.2	100.9±3.2	105.7±3.1$^{*,\$}$	0.02	97.2±2.0	101.2±2.1	106.7±2.3$^{*,\$}$	0.03	102.5±4.1	109.1±2.1$^{\#}$	103.7±3.1*	0.42
Total cholesterol (mg/dl)	209.3±6.1	204.4±4.8	199.2±6.2	0.18	203.4±3.2	205.7±4.0	198.1±2.9	0.56	203.3±6.3	205.9±4.9	199.7±7.2	0.19
LDL-cholesterol (mg/dl)	126.3±3.2	122.9±42	120.1±4.9	0.26	125.1±3.9	127.3±3.2	122.2±3.9	0.65	125.3±3.9	127.9±4.3	121.7±4.2	0.28
HDL-cholesterol (mg/dl)	57.3±2.1	55.1±1.2	48.6±3.1$^{*,\$}$	0.01	56.6±2.6	55.9±2.8	50.2±1.7$^{*,\$}$	0.02	49.7±2.1	56.1±1.9$^{\#}$	58.1 ±2.0*	0.01
Triglycerides (mg/dl)	111.9±9.1	115.4±9.0	134.9±8.2$^{*,\$}$	0.02	110.5±8.1	118.7±6.1	135.8±8.3$^{*,\$}$	0.01	133.2±5.2	115.9±8.0$^{\#}$	110.2±5.1*	0.01
CRP (ng/dl)	5.1±2.0	6.0±1.8	6.9±1.1$^{*,\$}$	0.03	4.6±1.1	6.0±0.9	7.3±1.0$^{*,\$}$	0.02	7.8±2.0	5.2±1.1$^{\#}$	4.8±1.0*	0.03
Insulin (mUI/l)	12.6±2.1	12.7±1.8	17.1±1.3$^{*,\$}$	0.01	12.4±1.2#	13.2±1.0	17.9±1.2$^{*,\$}$	0.02	15.6±1.1	12.5±1.0$^{\#}$	12.7±1.3*	0.02
HOMA-IR	3.0±0.4	3.1±0.5	4.7±0.9$^{*,\$}$	0.02	2.9±0.3	3.2±0.7	4.9±0.8$^{*,\$}$	0.01	4.3±0.2	3.2±0.5$^{\#}$	3.0±0.5*	0.03
IL-6	1.7±0.3	2.0±0.2	3.8±0.5$^{*,\$}$	0.03	1.7±0.1	2.9±0.3	4.2±0.4$^{*,\$}$	0.02	3.1±0.2	1.5±0.4$^{\#}$	1.1±0.9*	0.03

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference. *p*-values ANOVA Snedecor-F test. Post hoc Bonferroni test. *Statistical differences between tertile 3 and tertile 1. $^{\$}$ Statistical differences between tertile 3 and tertile 2. $^{\#}$Statistical differences between tertile 2 and tertile 1.

Table IV. Metabolic syndrome percentage and criteria of MS percentages by tertiles (FFM, FFMi, FFM%) (mean±SD).

Parameters	Total fat-free mass				Fat-free mass index				Fat-free mass percentage			
	Tertile 1	Tertile 2	Tertile 3	*p*	Tertile 1	Tertile 2	Tertile 3	*p*	Tertile 1	Tertile 2	Tertile 3	*p*
Percentage of MS	34.5%	43.2%[#]	47.8%[*]	0.01	27.3%	47.1%[#]	56.0%[*]	0.001	50.3%	45.8%[#]	32.5%[*]	0.001
Percentage of central obesity	58.0%	82.3%[#]	94.2%[*]	0.01	56.6%	88.9%[#]	95.6%[*]	0.005	83.3%	72.8%[#]	66.4%[*]	0.01
Percentage of Hypertriglyceridemia	3.2%	11.6%[#]	14.6%[*]	0.02	2.3%	13.2%[#]	16.3%[*]	0.02	13.6%	10.9%	5.9%[*]	0.02
Low HDL cholesterol	19.4%	19.6%	30.9%[*,$]	0.03	21.9%	21.3%	29.3%[*,$]	0.03	27.7%	23.7%	18.3%[*,$]	0.03
Percentage of Hypertension	39.0%	43.2%[#]	44.4%[*]	0.001	33.5%	42.9%[#]	55.0%[*]	0.01	52.5%	41.2%[#]	23.5%[*]	0.01
Percentage of hyperglycemia	11.1%	18.2%[#]	27.7%[*,$]	0.21	13.1%	20.6%[#]	26.0%[*]	0.02	21.8%	20.2%[#]	11.6%[*,$]	0.03

[*]Statistical differences between tertile 3 and tertile 1. [$]Statistical differences between tertile 3 and tertile 2. [#]Statistical differences between tertile 2 and tertile 1. MS: metabolic syndrome.

Table V. Odds ratio for Metabolic syndrome and components per tertiles.

Parameters	Total fat-free mass			Fat-free mass index			Fat-free mass percentage		
	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Percentage of MS	–	OR=1.45, 95% CI=1.08-1.94*	OR=1.74, 95% CI=1.26-2.41*	–	OR=2.37, 95% CI=1.75-3.20*	OR=3.38, 95% CI=2.42-3.72*	–	OR=0.68, 95% CI=0.51-0.91*	OR=0.29, 95% CI=0.20-0.41*
Percentage of central obesity	–	OR=3.36, 95% CI=2.40-4.70*	OR=11.8, 95% CI=6.6-20.1*	–	OR=4.39, 95% CI=2.60-5.31*	OR=12.7, 95% CI=6.4-21.3*	–	OR=0.54, 95% CI=0.38-0.76*	OR=0.39, 95% CI=0.27-0.57*
Percentage of Hypertriglyceridemia	–	OR=3.92, 95% CI=2.03-7.56*	OR=5.14, 95% CI=2.62-10.01*	–	OR=4.99, 95% CI=2.36-9.20*	OR=6.01, 95% CI=2.82-11.3*	–	OR=0.77, 95% CI=0.46-1.31	OR=0.40, 95% CI=0.23-0.68*
Low HDL cholesterol	–	OR=1.16, 95% CI=0.80-2.03	OR=2.09, 95% CI=1.42-3.09*	–	OR=0.96, 95% CI=0.69-1.36	OR=2.33, 95% CI=1.67-4.11*	–	OR=0.87, 95% CI=0.61-1.58	OR=0.56, 95% CI=0.38-0.82*
Percentage of Hypertension	–	OR=1.30, 95% CI=1.02-2.13*	OR=1.35, 95% CI=1.05-1.94*	–	OR=1.41, 95% CI=1.06-2.18*	OR=1.46, 95% CI=1.28-2.01*	–	OR=0.63, 95% CI=0.47-0.85*	OR=0.28, 95% CI=0.19-0.41*
Percentage of hyperglycemia	–	OR=1.26, 95% CI=1.05-2.25*	OR=2.10, 95% CI=1.40-3.28*	–	OR=1.31, 95% CI=1.16-2.43*	OR=2.31, 95% CI=1.28-3.40*	–	OR=0.91, 95% CI=0.63-1.31	OR=0.47, 95% CI=0.30-0.74*

*$p<0.05$ MS: metabolic syndrome.

Discussion

The main finding of this study is that the way to express fat-free mass (FFM) significantly influenced the direction of its association with Metabolic syndrome (MS) prevalence ant its components. This result is very important taking to account the increased risk for DM2 and MS and the largely purported idea that a greater FFM is beneficial for metabolic health, with a parallel increase in the use of impedanciometry to assess body composition.

Our results explain the discrepant data previously published in the literature between the association of FFM and MS, suggesting that the representation of FFM can explain these contradictions[11-17]. The benefit of normalizing FFM relative to squared height is that it better considers the impact of stature, which then allows to better compare individuals of different size and ethnicity[11]. While the percentage of FFM (FFM%) is a representation of body composition.

Our present data agree with those of others[4,17]. For example, Park and Yoon[4] showed opposite relationships between FFM and MS relating on how FFM was showed. These authors reported a positive association of FFM relative to height and a negative association of FFM relative to height[4,17]. These associations with MS among the different representations of FFM might be explained by the mediating role played by fat mass (FM). Scott et al[17] hypothesized that greater FFMi was positively correlated with FM and that the adipose tissue could increase the risk of having the MS. Furthermore, representing FFM as a percentage of body weight inherently represents FM and it is a good indicative of tissue distribution, not FFM per se. Thus, FFM% can assuredly predict metabolic diseases, but perhaps it is not adequate to isolate the direct role of FFM on MS. For example, Lee et al[6] concluded that muscle mass plays a protective role against future metabolic deterioration based on FFM%. Moreover, in their investigation FFM was similar between subjects progressing towards an unhealthy phenotype and those remaining in a healthy metabolic status.

Our data demonstrate a greater odds ratio of having MS and its components in the highest FFMi and FFM tertiles and the lowest FFM% tertiles. Some previous studies[4,24-27] concluding to a protective effect of greater FFM on metabolic status using FFM% in their designs and a deleterious association between FFMi and MS, specifically in females[5,12-15,28-30].

The negative association between FFM and MS could be explained by three hypotheses. First, a greater FFM is related with higher proportions of muscle type 2 fibers, these fibers have a lower oxidative ratio and a lower glucose-handling capacity compared with muscle type 1 fibres[31]. Second, lipids could infiltrate muscle, this fact alters the insulin cascading pathways[32]. Finally, a low capillary-to-fiber ratio and reduced capillary density in subjects with a higher FFM could also influence the association with MS secondary to reduced exchange area and blood flow have been linked with insulin resistance[33].

In a context where the incidence of metabolic syndrome is increasing worldwide, this present investigation has a high interest. We need to have accurate measurements of muscle mass to be able to have adequate nutritional interventions that improve muscle mass, since this increase in muscle mass decreases the risk of MS progression[7]. MS is a cluster of factors that include central adiposity, hypertension, dyslipemia, low levels of HDL-cholesterol and hyperglycemia, and is often accompanied by a proinflammatory status. This inflammation environment is recognized to be involved in the pathogenesis of insulin resistance. Skeletal muscle comprises a large percentage of body mass and is the most abundant insulin-sensitive tissue[34]. Additionally, subjects with low FFM have a low-grade inflammation status and it has been related with MS[35-36]. For example, Buchmann et al[35] showed a negative association of interleukin-6 and C reactive protein with FFM. In addition, when MS progresses and type 2 diabetes mellitus appears, an excess loss of muscle mass has been shown, thus further worsening the metabolic situation[36].

Limitations

Our study has some limitations. Firstly, the design has been realized only in Caucasian obese females, so the data are not generalizable to males, children, overweight subjects, or other ethnicities. Secondly, the investigation as a cross-sectional design does not allow producing causality. Thirdly, selection bias is likely because our study was single hospital based. Moreover, we measured whole-body FFM, some observations suggest that upper-body and lower-body FFM may not have the same influence on metabolic status[28]. Finally, in our study, we have not determined muscle functionality or strength, these parameters are also important given the relationship detected in some studies with worse muscle quality in patients with MS[37].

Conclusions

In summary, the prevalence of MS relative to FFM varies depending on the method used to represent it. FFMi and FFM have a positive relation and FFM% has a negative association. Further studies are necessary to evaluate these indexes in other risk populations and apply it in real clinical practice, in order to prevent MS and sarcopenia. These two entities adversely affect quality of life, morbidity and mortality.

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Ethics Approval
This study protocol was reviewed and approved by [HCVUA Committee], approval number [No. 6/2021]. This research complies with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki.

Informed Consent
Written Informed consent was obtained from all individual participants included in the study.

Availability of Data and Materials
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflict of Interests
The authors have no conflicts of interest to declare.

Authors' Contributions
Daniel Antonio de Luis and Alfredo Martinez designed the study an wrote the article.
Juan Jose Lopez Gomez and Olatz Izaola, realized nutritional evaluation.
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