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Original article

The decline in muscle strength and muscle quality in relation to metabolic derangements in adult women with obesity

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SUMMARY

Background & aims: The metabolic and functional characteristics related to sarcopenic obesity have not been thoroughly explored in the earlier stages of the aging process. The aim of the present study was to examine the phenotype of sarcopenic obesity, in terms of lean body mass, muscle strength and quality, in adult women with and without the Metabolic Syndrome (MetS), and its relationship with the features of myosteatosis.

Methods: Study participants were enrolled at the Sapienza University, Rome, Italy. Body composition was assessed by DXA. The Handgrip strength test (HGST) was performed. HGST was normalized to arm lean mass to indicate muscle quality; intermuscular adipose tissue (IMAT) and intramyocellular lipid content (IMCL) were measured by magnetic resonance imaging and spectroscopy, as indicators of myosteatosis. Different indices of sarcopenia were calculated, based on appendicular lean mass (ALM, kg) divided by height squared, or weight. The NCEP-ATPIII criteria were used to diagnose the MetS. HOMA-IR was calculated. The physical activity level (PAL) was assessed through the IPAQ questionnaire.

Results: 54 women (age: 48 ± 14 years, BMI: 37.9 ± 5.4 kg/m^2) were included. 54% had the MetS (metabolically unhealthy, MUO). HGST/arm lean mass was lower in MUO women than women without the MetS (6.3 ± 1.8 vs. 7.8 ± 1.6, $p = 0.03$). No differences emerged in terms of absolute ALM (kg) or other indices of sarcopenia (ALM/h^2 or ALM/weight) between metabolically healthy (MHO) vs. MUO women ($p > 0.05$). Muscle quality was negatively associated with HOMA-IR ($p = 0.02$), after adjustment for age, body fat, hs-CRP levels, and PAL. IMAT, but not IMCL, was significantly higher in obese women with the MetS compared to women without the MetS ($p > 0.05$). No association emerged between HGST/arm lean mass and IMAT or IMCL when HOMA-IR was included in the models.

Conclusion: Insulin resistance, and not sarcopenia or myosteatosis *per se*, was associated with muscle weakness, resulting in the phenotype of "dynapenic obesity" in middle-aged women with the metabolic syndrome.

1. Introduction

In recent years growing interest has been directed to sarcopenic obesity, given the parallel increase of obesity and life expectancy in Western countries [1,2]. Alterations in body compartments are strictly linked to energy imbalance, though multiple factors interfere with energy partitioning and the consequent changes in body composition (e.g. hormone dysregulations, insulin-resistance, inflammation, etc.) [3,4]. Even keeping weight stable, a relatively precocious decline in lean body mass has been reported, starting after the third decade [5,6].

Concurrently, body fat tends to redistribute from the subcutaneous toward the visceral depots [7]. Indeed, the presence of obesity can precipitate and exacerbate the changes in body compartments. However the presence of excess fat and reduced lean mass partially depicts the complex phenotype of sarcopenic obesity: in fact the hallmarks of this syndrome encompass an array of clinical aspects, mainly represented by functional impairment and mobility limitations [8–10]. In addition, accumulating

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evidence pointed out a tight connection between sarcopenia, sarcopenic obesity and metabolic alterations such as the metabolic syndrome [11]. Insulin resistance in obese individuals may be responsible for the development of sarcopenia through the interference with protein anabolism and protein breakdown leading to the decrease of lean body mass [12,13]; in turn, reduced skeletal muscle quantity favors insulin resistance, being skeletal muscle the major target tissue of insulin action [14]. Nevertheless, muscle atrophy is only a partial contributor to functional features of sarcopenia, such as weakness, namely dynapenia, and poor functionality and performance [15–17]. Muscle quality, defined as strength generated per unit of muscle mass, has been recognized to perform better than absolute muscle strength in predicting global functional capacity [18,19]. Notably, Newman et al. demonstrated that muscle strength represents a robust predictor of mortality in older individuals, regardless of low lean mass [20]. Importantly, due to its easiness of measurement in the clinical setting, grip strength was validated against leg strength, with analogous and overlapping predictive ability for mortality risk [20].

Furthermore, as shown in previous studies including elderly participants, age-related ectopic fat infiltration within skeletal muscle affects muscle contractility and strength generation [21–23]. On the other hand, just few studies examined the connection between ectopic lipid storage within myocytes (based on muscle biopsy or magnetic resonance spectroscopy) and strength [24,25].

The majority of studies investigating metabolic and functional correlates of sarcopenia and sarcopenic obesity were conducted in the geriatric population, whereas evidence is scarce regarding the adult population.

Thus, the aims of the present study were: to investigate the presence of the phenotypic aspects of sarcopenia, in terms of muscle quantity: reduced skeletal muscle mass (at whole body level and segmental level), and muscle quality: reduced muscle strength (dynapenia), and to examine the relationship between muscle strength, muscle quality and features of myosteatosis (ectopic fat storage in skeletal muscle as intermuscular adipose tissue, “IMAT”, that is adipose tissue beneath the muscle fascia and between muscle groups, and lipid droplet deposition in myocytes as intramyocellular lipid content “IMCL”) in metabolically healthy (MHO) and metabolically unhealthy (MUO) adult women with obesity.

2. Materials and methods

Study participants were recruited at the “CASCO” High Specialization Center for the Care of Obesity, Policlinico “Umberto I” Hospital, Sapienza University, Rome, Italy. Inclusion criteria were: age >18 and <65 years, body mass index (BMI) $\geq$ 30 kg/m^2, ethnicity: Caucasian Italian subjects. As exclusion criteria, we considered: any malignant diseases during the last 5 years, any inflammatory or autoimmune diseases, corticosteroids for systemic use, any medications potentially affecting body weight or body composition, syndromic obesity, participation in a reducing-weight program in the last three months, renal failure, heart failure, any type of diabetes, history of viral or autoimmune liver diseases or any other chronic liver disease, excessive alcohol intake (>70 g/week for women), any neurodegenerative diseases, or any musculoskeletal diseases. The study protocol was approved by the Ethical Committee of the “Sapienza” University, Rome, Italy. Written informed consent was obtained from all the participants. All subjects underwent a complete physical examination. Anthropometric measurements. Body weight, height, waist circumference were measured following standardized procedures [26]. The same tools were used in all subjects: a SECA scale 86 (200 kg, to the nearest 0.1 kg), a flexible metallic tape (200 cm, to the nearest 0.1 cm), a telescopic stadiometer (200 cm; to the nearest 0.1 cm). Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). Definition of obesity. Obesity was defined as BMI $\geq$30 kg/m^2. Body composition analysis. Fat mass (FM) and fat-free mass (FFM) were assessed by dual-energy X-ray absorptiometry (DXA) (Hologic 4500 RDR), with coefficient of variation < 1.5% for FM and FFM. Appendicular lean mass (ALM) was evaluated by DXA and calculated as the sum of lean soft tissue masses of arms and legs [27]. Biochemistry. Blood samples were collected after an overnight fast. The following biochemical parameters were assayed: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, glucose and insulin, serum high-sensitivity C-reactive protein (hs-CRP) levels, using commercial kits. Glucose metabolism and insulin resistance. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting plasma insulin and glucose levels using the formula: insulin $\times$ glucose/405 (mU/l $\times$ mg/dl). Also the HOMA-β index was calculated [insulin (mU/l) $\times$ 360/glucose (mg/dl) $-$ 63] [28]. Definition of the metabolic syndrome (MetS). MetS was diagnosed in accordance with the criteria proposed in the National Cholesterol Education Program- Third Adult Treatment Panel [29]. The Handgrip strength test (HGST) was performed according to the standardized procedure [30,31], using a digital dynamometer (DynEx, Akern, Pontassieve, FI, Italy). For each participant, 3 measurements on the dominant hand were averaged. Moreover, the mean value obtained was normalized to DXA-derived arm lean mass, similar to previous studies [32,33], and was used in the statistical analysis, as a proxy of muscle quality [18,34]. Indices of sarcopenia and sarcopenic obesity. Different indices of sarcopenia were calculated, based on appendicular lean mass (ALM, kg) divided by height squared (ALM/h^2), or weight (ALM/weight), and prevalence of sarcopenia was defined according to the afore mentioned indices, using cutpoints calculated for the Italian population [10]. Due to the large variability in prevalence data and the lack of a consensus on the criterion to be used, we considered the indices of sarcopenia as continuous variables for further analysis [35,36]. Intermuscular adipose tissue (IMAT, please see below for methods) was divided by thigh muscle CSA in order to obtain an index of segmental sarcopenic obesity, modified from Tuttle et al. [37]. The physical activity level (PAL) was assessed through the administration of the International Physical Activity Questionnaire (IPAQ) [38].

3. Magnetic resonance (MR) imaging and spectroscopy

Data were acquired on a 3T magnet (GE Discovery 750; General Electric Healthcare, Milwaukee, WI) with a peak gradient amplitude of 50 mT/m, a time to peak of 200 μsec In each examination, subjects lay in a supine position with both legs placed along the axis of the coil and immobilized by firm padding. Spectra were obtained from the vastus lateralis of right leg, using a point-resolved spectroscopy sequence (PRESS) with a repetition time (TR) of 1500 and echo time (TE) of 30 ms. A 20 mm^3 voxel was positioned within the muscle, using a T1-weighted sequence for localization, containing as little as possible visible interstitial tissue or fat, to avoid contamination from EMCL. The acquisition time was of approximately 24 s. Field homogeneity was automatically adjusted for each voxel. T2 relaxation times of both metabolites were determined from their peak amplitudes at each echo time using an exponential least-squares fitting algorithm; saturation bands were used The number of signal averages was 8 and the spectral collection time was 3 ms. For the quantification of subcutaneous and visceral adipose tissue (SAT and VAT), a 3D GRE T1-weighted sequence in the axial plane (TR, 4.2; TE, 1.3; FA, 15°; matrix, 320 $\times$ 192; section thickness, 5 mm, reconstructed 2.5 mm; intersection gap, 0) was

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acquired with the IDEAL imaging and reconstruction method, which enabled the separation between water and fat components using the chemical shift MR technique.

MR spectra were reconstructed on a dedicated workstation with SAGE Dev2 0017.1 software (General Electric Healthcare, Milwaukee, WI). Raw data were zero-filled once, and no filter was used. The data were phase-corrected, Fourier-transformed, baseline-corrected and averaged. A Marquardt curve-fitting procedure was performed using a Lorentzian function to calculate the area under the fat and water peaks. Spectra referenced the residual water and IMCL-(CH2), and IMCL-(CH3) peaks at 4.7 ppm and 1.3, and 0.9 ppm respectively. IMCL content was expressed as a percentage of the water signal [39].

Fat-only datasets from T1-weighted LAVA sequences were transferred to a personal computer and analyzed using a commercially available software package (Slice-O-Matic; Tomovision Inc.; Montreal, Canada) and a procedure that has been previously described [40]. VAT and SAT were calculated at L4-L5 by drawing a free-form ROI and manual thresholding values. Intermuscular adipose tissue (IMAT) was assessed as described by Boettcher et al. [41].

4. Statistical analysis

Distributions of continuous variables were examined for skewness and kurtosis, and were logarithmically transformed when appropriate to adjust distributional patterns. Log-transformed variables are presented as untransformed values for ease of reading. Differences between MHO and MUO women were examined using Student's t test, and ANCOVA was used for adjustments for the variables specified in the text and tables. Pearson χ^2 was used for the comparison of the distribution of categorical variables. Pearson's correlation was used to examine the relationship between variables. Multiple linear regression analyses were used to examine association between muscle strength/quality and the variables included in the models. The covariates included in the models were chosen a priori among those factors expected to influence the dependent variable, based upon biological mechanism or evidence from research; they are specified in the results section. The level of significance for all statistical tests was set at $p < 0.05$. Data analyses were performed using IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY).

5. Results

54 women (age: 48 ± 14 years, BMI: 37.9 ± 5.4 kg/m^2) were included. 29 out of 54 (54%) had the MetS (metabolically unhealthy). Demographic and anthropometric characteristics are shown in Table 1.

Prevalence of menopause and smoking habit were not significantly different between the MHO group vs. the MUO group; no difference emerged between groups concerning the physical activity level.

As displayed in Table 2, women in the MUO group exhibited (by definition) higher diastolic blood pressure, glucose, triglyceride, and insulin levels than their MHO counterparts, after adjustment for age and VAT. Also HOMA-IR was significantly higher in MUO women than MHO women ($p = 0.02$), whereas HOMA-β was not different between groups. No differences were observed in waist circumference, systolic blood pressure, or hs-CRP levels.

Body composition, muscle fat infiltration and lipid storage, and MetS. With respect to body composition, no differences were observed between groups in terms of fat mass in absolute value, body fat percentage, total lean body mass, and appendicular lean mass in absolute value (Table 3).

MR-imaging revealed that VAT and IMAT were significantly higher in the MUO group vs. MHO group $p = 0.002$ and $p = 0.04$, respectively), whereas SAT, IMCL, and thigh muscle CSA were not significantly different between groups;

Indices of sarcopenia and MetS. The prevalence of sarcopenia in the present obese female cohort was highly variable according to the different criteria used (no participant was identified as sarcopenic according to the definition based on ALM/h^2, whereas the criterion for the index ALM/weight led to a prevalence rate of 52.6%). Due to that large discrepancy, we compared the different indices as continuous variables. Indices of sarcopenia were not significantly different between groups after adjustment for age (ALM/h^2: 9.26 ± 1.72 kg/m^2 in the MHO group vs. 9.17 ± 1.19 kg/m^2 in the MUO group, $p = 0.95$; ALM/weight: 0.246 ± 0.017 in the MHO group vs. 0.239 ± 0.021 in the MUO group, $p = 0.22$), save the segmental index of sarcopenic obesity (IMAT normalized to thigh muscle CSA) was higher in MUO women than MHO participants (0.255 ± 0.334 vs. 0.152 ± 0.068, $p = 0.03$ after adjustment for age).

Muscle strength, muscle quality, and MetS. Muscle strength (HGST in absolute value, MUO group: 16.9 ± 4.6 vs. MHO group: 20.6 ± 4.9, $p = 0.008$) and muscle quality (HGST normalized to arm lean mass) were lower in MUO women than women without the MetS (6.3 ± 1.8 vs. 7.8 ± 1.6, $p = 0.001$, remaining significant also after adjustment for age: $p = 0.03$). Right arm lean mass was not different between groups (MUO group: 2.8 ± 4.6 vs. MHO group: 2.7 ± 0.5, $p = 0.43$) (Fig. 1).

Muscle quality and insulin resistance. Multiple linear regression analysis revealed that HGST/arm lean mass was negatively associated to HOMA-IR ($\beta = -0.37$, SE = 0.16, $p = 0.02$), after adjustment for age, body fat, hs-CRP levels, and PAL (Fig. 2).

Table 1
Demographic and anthropometric characteristics of study participants.

	MHO group	MUO group	p
	n = 25	n = 29	
Age (years)	45.4 ± 13.2	51.3 ± 13.9	0.08
BMI (kg/m^2)	37.4 ± 6.2	38.4 ± 4.6	ns*
PAL^ (METs·min·week)	3821 ± 5923	2664 ± 3028	ns*
Menopause (%)	20.4	29.6	ns
Smokers (%)	14.3	28.6	ns

Legend: BMI: Body Mass Index; PAL: Physical Activity Level (International Physical Activity Questionnaire Score); MET: Metabolic Equivalent; ^ log-transformed variable; *p adjusted for age.

Table 2
Anthropometric, metabolic characteristics, and inflammation.

	MHO group	MUO group	p*
	n = 25	n = 29	
Waist circumference^(cm)	117.5 ± 25.3	116.2 ± 11.0	ns§
Systolic BP (mmHg)	125 ± 14	133 ± 14	0.07
Diastolic BP (mmHg)	80 ± 10	86 ± 9	0.04
Triglycerides^ (mg/dl)	100 ± 30	153 ± 72	0.04
HDL- cholesterol (mg/dL)	55 ± 9	50 ± 13	ns
Glucose^ (mg/dl)	89 ± 6	107 ± 18	0.01
Insulin^ (uU/ml)	9.1 ± 4.5	14.1 ± 6.5	0.03
HOMA-IR^	2.03 ± 1.04	3.97 ± 3.5	0.02
HOMA-β	131 ± 57	139 ± 54	ns
Hs-CRP^ (ug/l)	3544 ± 2360	6493 ± 2220	ns

Legend: MHO: metabolically healthy obese; MUO: metabolically unhealthy obese; BP: blood pressure; HDL: high-density lipoprotein; HOMA-IR: Homeostasis Model Assessment- Insulin Resistance; Hs-CRP: high-sensitivity C-reactive protein; ^ log-transformed variables; *p adjusted for age and VAT(visceral adipose tissue). §p adjusted for age.

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Table 3
Body composition and adiposity.

	MHO group	MUO group	p*
	n = 25	n = 29	
DXA			
Body fat (%)	40.2 ± 2.9	40.0 ± 4.3	ns
FM (kg)	39.1 ± 8.4	38.0 ± 8.3	ns
LBM (kg)	55.4 ± 10.0	54.0 ± 8.4	ns
ALM (kg)	23.9 ± 4.7	22.6 ± 3.5	ns
MRI			
VAT^ (mm^2)	9414 ± 3639	18129 ± 17,357	**0.002**
SAT^(mm^2)	51,173 ± 12,034	67,888 ± 99,936	ns
Thigh muscle CSA^(mm^2)	10,893 ± 1690	10,747 ± 1801	ns
IMAT^ (mm^2)	1614 ± 642	2655 ± 3710	**0.04**
MRS			
IMCL^ (%)	21.5 ± 23.9	27.4 ± 26.6	ns

Legend: MHO: metabolically healthy obese; MUO: metabolically unhealthy obese; DXA: Dual-energy X-ray absorptiometry; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; FM: fat mass; LBM: lean body mass; ALM: appendicular lean mass; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; CSA: cross-sectional area; IMAT: intramuscular adipose tissue; IMCL: intramyocellular lipid content; ^ log-transformed variables; *p adjusted for age; ns: not significant.

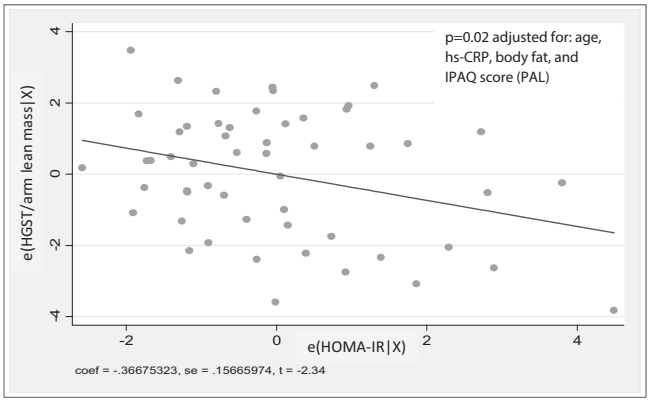

Fig. 2. Association between muscle quality and insulin resistance. Legend: HGST: handgrip strength; HOMA-IR: Homeostasis Model Assessment- Insulin Resistance; Hs-CRP: high-sensitivity C-reactive protein; IPAQ: International Physical Activity Questionnaire; PAL: Physical Activity Level; SE: standard error.

Muscle quality, muscle fat infiltration and lipid storage. Muscle quality was inversely associated with IMAT ($\beta = -8.9*10^{-4}$, $SE = 3.9*10^{-4}$, $p = 0.03$) after adjustment for age, hs-CRP, and PAL, but significance was lost when HOMA-IR was included in the model. No association emerged between HGST/arm lean mass and IMCL.

6. Discussion

A wealth of studies focused on the age-related decline of lean body mass and muscle strength, with sarcopenia and dynapenia being a frequent combination in the geriatric population. However evidence is scarce in the adult population at the early stages of the aging process.

In the present study we provide evidence that adult women who were obese and metabolically unhealthy were weaker than their counterparts with good metabolic health, due to reduced muscle quality, despite no differences were detected between groups in terms of total or appendicular muscularity. In addition, also the indices of sarcopenia were not significantly different when women with the metabolic syndrome were compared to participants who were metabolically healthy, except for a segmental index of sarcopenic obesity. These findings are in line with prior studies showing that muscle strength drops at a faster rate than muscle mass [21]. In obese subjects, probably due to an adaptive mechanism counteracting the increased load of body fat, approximately one quarter of the excess weight consists of fat-free tissues [42]. Similarly, Forbes et al. reported an anabolic response in different hormonal axes to short-term overfeeding in female volunteers, leading to a substantial gain of both lean mass and fat mass [43]. One can hypothesize that, at least in the short or intermediate duration of obesity, the exposure to excess energy can contribute to a relative increase of the lean compartment, and only in the long-term the obesity-related low-grade inflammation could contribute to the deterioration of skeletal muscle mass leading to the phenotype of sarcopenic obesity [36,44]. Thus, in obese adults dynapenia may be present even in the absence of reduced LBM, and the classical "natural history" of age-related decrease in skeletal muscle mass and strength may follow different trajectories in obesity.

In accordance with Kotronen et al., women with the metabolic syndrome did not exhibit larger amount of IMCL than metabolically healthy women, though conflicting data have been reported

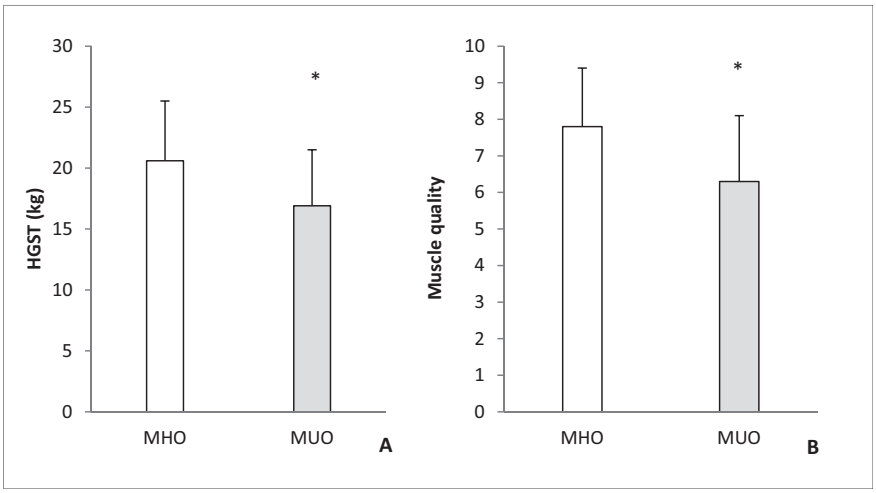

Fig. 1. Handgrip strength (HGST) and muscle quality in metabolically healthy (MHO) vs. metabolically unhealthy (MUO) women. *p < 0.05.

regarding the intramyocellular lipid accumulation related to the metabolic syndrome and type 2 diabetes [45].

Interestingly, in our study population we found no association between muscle strength/quality and fatty infiltration and lipotoxicity in the skeletal muscle (either IMAT or IMCL) when multiple regression analyses accounted for insulin resistance in the models.

Longitudinal data do not seem to be conclusive regarding the relationship between weakness and fat accumulation within skeletal muscle. Our observations are in agreement with findings from a 5-year follow-up of the participants in the Health ABC study, in whom the increase in muscle fat infiltration at the midthigh computed tomography (CT) scan was not related to changes in muscle strength (examined by isokinetic leg muscle torque) in both sexes. When data analysis was performed according to weight change, fatty infiltration of the skeletal muscle only predicted the drop in muscle strength in male elders who remained weight stable [21]. Conversely, our results are in disagreement with prior studies conducted in the geriatric population, demonstrating a detrimental role of fatty infiltration on functional parameters [22]. In addition, Visser et al. found that elders with larger mid-thigh muscle fat infiltration evaluated by CT exhibited higher incidence of mobility disability over a 2.5 year follow-up period [23].

Concerning the nexus between functional capacity and excess lipid storage within muscle, only a minority of studies assessed IMCL through magnetic resonance spectroscopy or muscle biopsy [24,25]. Moreover, extant studies provided with conflicting findings, and the effect of IMCL on muscle contractility and strength generation remains to be further elucidated.

Based on *in vitro* experiments, Choi et al. demonstrated that intramyocellular lipids were inversely related to fiber contractility in older participants who underwent muscle biopsy of the vastus lateralis [24]. The lack of association between muscle strength or muscle quality and IMCL in our study population is somewhat in agreement with findings from a Japanese study in which no significant correlation was shown between IMCL and strength produced during isometric knee extension in older men and women (mean age 70 years); conversely, in the same study a negative relationship linked IMCL and strength in the young group (mean age: 20 years) [25]. To which extent the lipid content in myocytes interferes with muscle contractile properties, possibly influencing internal resistance or other mechanical properties, deserves future investigations in the normal weight as well as obese population.

Regardless of IMCL amount, IMCL composition (e.g. lipid classes frequently associated with lipotoxicity, such as ceramides) could be responsible for alterations underpinning muscle weakness. In fact Ferreira and coll. clearly showed that enhanced sphingomyelinase activity, leading to excess ceramide production, was able to activate a pro-oxidant cascade resulting in impaired contractility and to precocious onset of muscular fatigue [46]. Furthermore, ceramides and other toxic lipid species, such as diacylglycerol, have been acknowledges as relevant mediators in the pathogenesis of lipid-induced insulin resistance in obesity and in type 2 diabetes [47,48].

In addition, oxidative stress related to lipotoxicity in the skeleletal muscle is also responsible for alterations in both neurological and muscular properties. In more detail, the accumulation of reactive oxygen species has been identified as a major player in the impairment of muscle fiber activation and the disruption of the excitation-contraction coupling, resulting in loss of strength [49].

Though the hypothesis of the deleterious effects of lipid intermediates appears plausible, additional factors not examined in our study could have contributed to our findings: Gaster et al. demonstrated that the reduced expression of the glucose transporter protein GLUT4 in obese and type 2 diabetic patients is dependent on the volume of muscle fibers [50]. So we have to acknowledge that the lack of specimens from muscle biopsies represents the main limitation to our study, preventing the evaluation of the type and the volume of muscle fibers, and lipid composition within myocytes.

However, the point of strength of our study was indeed the multidimensional assessment of the complex phenotype that is sarcopenic obesity in terms of body composition, metabolic alterations, and functional outcomes.

7. Conclusion

Insulin resistance, and not myosteatosis or sarcopenia *per se*, was associated with reduced muscle strength and quality, resulting in the phenotype of “dynapenic obesity” in middle-aged women with the metabolic syndrome. Greater attention should be paid to functional consequences related to insulin resistance, as reduced muscle strength has been associated with increased CVD risk and mortality [51,52].

Disclosure of interest

None Declared.

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