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SARCOPENIC OBESITY AND METABOLIC SYNDROME IN ADULT CAUCASIAN SUBJECTS

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Abstract: *Objectives:* Recently metabolic aspects linked to sarcopenic obesity (SO) were investigated. Extant studies involved especially older people from Asian or White-mixed American cohorts. The aims of our study were: to explore the prevalence of sarcopenia in Caucasian adult obese subjects using two different indices of sarcopenia, and to investigate the relationship among SO, metabolic syndrome (MS), inflammation, and serum albumin concentrations. *Design:* Cross- sectional study. *Subjects/methods:* The study was performed from 2011 to 2014 in a hospitalized care setting. Inclusion criteria were: age>18 and <65 years, BMI≥30 Kg/m^2. Fat mass (FM) and fat-free mass (FFM) were assessed by DXA. Appendicular skeletal muscle mass (ASMM) was calculated. Sarcopenia was defined as ASMM/height^2 or ASMM/weight <2SD than the sex-specific mean of a young population. The cutoffs were ASMM/h^2<6.54 Kg/m^2 for men and 4.82 Kg/m^2 for women, and ASMM/weight<0.2827 for men and 0.2347 for women. ISI-Matsuda was calculated. MS was diagnosed (NCEP-ATPIII). *Results:* 727 subjects (age: 45.72±13.56 years, BMI: 37.74±5.82 kg/m^2) were enrolled. The prevalence of SO was 1.0% or 34.8% in men and 0.6% or 50.1% in women, using ASMM/height^2 ratio or ASMM/weight. Subjects with SO based on ASMM/height^2 were scarce, only data relying on ASMM/weight were considered. Subjects with SO had higher BMI, waist circumference, FM, and lower FFM and ASMM than nonsarcopenic obese individuals (all p<0.05). ISI-Matsuda was lower and hs-CRP levels were higher in subjects with SO (all p<0.05). MS was more prevalent in subjects with SO than nonsarcopenic obese subjects (47.6% vs 34.3%, p<0.001). ASMM/weight was decreased in subjects with MS (0.2522±0.0410 vs 0.2423±0.0352, p=0.001). *Conclusion:* SO is associated with MS and low- grade inflammation in adult Caucasian subjects. Metabolic profile evaluation should be recommended in subjects with SO.

Key words: Sarcopenic obesity, insulin sensitivity, metabolic syndrome, low-grade inflammation.

Introduction

In the last years, a wealth of studies focused on changes in body composition associated with aging (1-3). After the third decade, even in case of stable weight, lean body mass tends to decrease while relative fat mass increases (2-5). This process is exaggerated in presence of obesity as well as sedentary habits or unhealthy dieting (2, 6-7). In particular, excess fat mass worsens disability by increasing total body mass and exacerbating muscle fat infiltration (2, 8-9). Most studies were carried out in the elderly population, highlighting functional impairment linked to sarcopenic obesity (10). Recently also metabolic aspects related to sarcopenic obesity were investigated, considering that insulin resistance and inflammation were described as the major actors in the pathogenesis of this syndrome (8, 11). Other than metabolic and functional implications, an important issue is represented by the lack of a universally accepted definition of sarcopenia as well as sarcopenic obesity (8, 12). Most frequently, authors used skeletal muscle mass or appendicular skeletal muscle mass standardized for height squared or body weight to define sarcopenia (8, 12- 14). From the extant literature, it seems that the ratio between appendicular muscle mass and body weight better captures metabolic characteristic of sarcopenia associated to obesity than the use of appendicular muscle mass divided by height squared (15). However, existing studies involved especially elderly people, and the indices of sarcopenia associated with obesity were used overall in Asian cohorts or White- mixed American, or Hispanic populations (16-21).

Considering that body composition changes are progressive with age, the coexistence of sarcopenia and obesity may be responsible for the precocious onset of clinical scenarios accounting for the synergistic effects of both conditions (5, 7). The clinical phenotype as well as the more appropriate definition of sarcopenic obesity need to be better clarified. Hence, the aims of our study were: to explore the prevalence of sarcopenia in Caucasian Italian adult (from young to pregeriatric age) obese subjects using two different indices of sarcopenia, and to investigate the relationship among sarcopenic obesity, metabolic syndrome and inflammation, and serum albumin concentrations.

Materials and methods

Study participants were recruited among subjects referring to the "CASCO" High Specialization Center for the Care

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of Obesity at the Department of Experimental Medicine, "Sapienza" University of Rome, Italy, from June 2011 to October 2014.

The following inclusion criteria were considered: age > 18 and < 65 years, body mass index (BMI) ≥ 30 Kg/m^2, ethnicity: Caucasian Italian subjects. In addition, participants had to be sedentary (did not participate in exercise more than twice per week) (22).

As exclusion criteria, we considered: any malignant disease during the last 5 years, any inflammatory or autoimmune disease, corticosteroids for systemic use, any medication 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 disease or any other chronic liver disease, excessive alcohol intake (>140g/ week for men and 70g/ week for women) (23).

The study protocol was approved by the Ethical Committee of the "Sapienza" University of Rome and written informed consent was obtained from all the participants.

All subjects underwent a multidimensional evaluation encompassing:

1. Complete physical examination.
2. Anthropometric measurements. Body weight, height, waist circumference were measured following the procedures described in the "Anthropometric standardization reference manual" (24). An inter- assessor alignment training session preceded the measurements. The same tools were used in all subjects: a SECA scale 86 (200 kg, to an accuracy of 0.1 Kg, certified and homologated as class III), a flexible metallic tape (200 cm, to an accuracy of 0.1 cm), a telescopic stadiometer (200 cm; to an accuracy of 0.1 cm). Body mass index (BMI) was calculated as body weight (Kg) divided by height squared (m^2).
3. Definition of obesity. Obesity was defined as BMI ≥ 30 Kg/ m^2.
4. 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 of < 1.5% for FM and LBM. Appendicular skeletal muscle mass (ASMM) was evaluated by DXA and calculated as the sum of lean soft tissue masses of arms and legs (25).
5. Definitions of sarcopenia. Two indices of sarcopenia were calculated: i) appendicular skeletal muscle mass (Kg) divided by height squared (m^2) (ASMM/ h^2) (13); ii) appendicular skeletal muscle mass (Kg) adjusted for body weight (Kg) (ASMM/ weight), as modified from previous studies (14, 15).

Sarcopenia was defined as ASMM/ h^2 or ASMM/ weight less than two standard deviations below the sex- specific mean of a young healthy reference Italian population (20- 39 years) (26). The cutoffs obtained from the reference group were: ASMM /h^2 < 6.54 Kg/m^2 for males and 4.82 Kg/m^2 for females (26), and ASMM/ weight < 0.2827 for males and 0.2347 for females. The cutoffs for ASMM/ weight in the Italian population are presented here for the first time.

6. Definition of sarcopenic obesity. Sarcopenic obesity was considered in case of coexistence of the abovementioned definitions of obesity and sarcopenia.
7. 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 albumin, serum highly sensitive C-reactive protein (hs- CRP) levels, using commercial kits.
8. Glucose metabolism and insulin resistance/ sensitivity. All participants underwent an oral glucose tolerance test (OGTT) considering both glucose and insulin response. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting plasma insulin and glucose levels using the formula: insulin × glucose/22.5 (mU/L×mmol/L) (27). Insulin sensitivity was assessed as the insulin sensitivity index (ISI) calculated using the OGTT values as proposed by Matsuda and DeFronzo (28).
9. Definition of metabolic syndrome (MS). MS was diagnosed in accordance with the criteria proposed in the National Cholesterol Education Program- Third Adult Treatment Panel (NCEP- ATP III) (29).

Statistical analysis

After verification of the normal distribution of the variables, parametric tests for comparison of means (Student's t-test and ANOVA) and tests for the evaluation of the frequency distribution (Pearson's χ^2 test) were performed. Differences were considered to be statistically significant for $p<0.05$. Statistical analysis was performed using SPSS 10.0 statistical software (SPSS Inc. Wacker Drive, Chicago, IL, USA).

Results

727 obese subjects were enrolled (141 males and 586 females, mean age: 45.63±13.53 and 45.76±13.58 years; mean BMI: 37.56±5.99 and 37.80±5.77 Kg/m^2, respectively).

The prevalence of sarcopenia was 1.0 % in men and 0.6% in women, according with definition based on ASMM/ height^2 ratio; when defined as ASMM/ weight, the prevalence of sarcopenia was 34.8% in men and 50.1% in women.

Taking into account that the number of subjects classified as sarcopenic using the ratio ASMM/ h^2 was scarce, we performed the statistical analysis considering only the classification of subjects based on ASMM/ weight.

Demographic, anthropometric, biochemical and inflammatory parameters of sarcopenic and nonsarcopenic obese subjects are described in Table 1.

In both genders, sarcopenic obese subjects were older and showed higher BMI, waist circumference, absolute fat mass,

Table 1
Demographic, anthropometric and biochemical parameters between sarcopenic obese subjects and nonsarcopenic obese subjects (sarcopenia defined as ASMM/weight)

	Males			Females		
	Sarcopenic obese subjects N= 68	**Nonsarcopenic obese subjects N= 73**	**p**	**Sarcopenic obese subjects N= 350**	**Nonsarcopenic obese subjects N= 236**	**p**
Age (years)	46.49±13.73	43.10±13.66	0.006	46.99±13.76	42.86±13.01	<0.001
Body weight (Kg)	117.71±17.44	107.30±14.47	0.677	99.99±16.71	94.43±14.48	0.021
BMI (Kg/m^2)	38.85±5.88	35.14±3.74	<0.001	38.84±5.79	36.03±4.92	<0.001
Waist circumference (cm)	124.31±11.63	114.70±12.38	<0.001	118.98±13.19	112.60±11.65	<0.001
FM (%)	34.57±3.65	28.38±5.95	<0.001	44.79±3.98	39.14±3.50	<0.001
FM (Kg)	40.17±6.54	30.78±8.69	<0.001	44.83±8.94	37.12±7.53	<0.001
FMI (Kg/m^2)	13.24±1.94	10.07±2.72	<0.001	17.42±3.27	14.16±2.66	<0.001
FFM (%)	65.43±3.65	71.62±5.95	<0.001	55.21±3.98	60.62±4.18	<0.001
FFM (Kg)	70.53±8.75	73.47±8.49	0.048	50.43±7.34	54.69±8.10	<0.001
FFMI (Kg/m^2)	23.25±2.42	24.06±2.43	0.047	19.60±2.59	20.86±2.75	<0.001
Truncal FM(%)	37.95±4.11	29.47±6.34	<0.001	45.37±4.76	38.33±4.49	<0.001
Truncal FM (Kg)	21.82±3.68	15.41±4.48	<0.001	21.80±4.65	17.74±8.16	<0.001
ASMM (Kg)	30.69±3.80	33.20±4.80	0.001	21.35±3.65	23.83±3.81	<0.001
ASMM/h^2 (Kg/m^2)	10.11±0.98	10.87±1.30	<0.001	8.29±1.23	9.09±1.28	<0.001
HOMA-IR	7.79±6.99	4.64±3.72	0.002	5.96±6.23	4.88±4.15	0.026
ISI- Matsuda	2.58±1.93	3.88±2.48	0.040	2.33±2.03	3.65±2.20	0.042
Albumin (g/dL)	4.20±0.39	4.42±0.38	0.002	4.11±2.29	4.62±1.12	0.041
Hs- CRP (mg/L)	0.43±0.14	0.33±0.16	0.029	0.74±0.41	0.60±0.32	0.028

Legend: BMI: body mass index; FM: fat mass; FFM: fat- free mass; FMI: fat mass Index; FFMI: fat- free mass index; ASMM: appendicular skeletal muscle mass; ASMM/h^2: appendicular skeletal muscle mass (Kg) divided by height squared (m^2); HOMA-IR: Homeostasis model assessment of insulin resistance; ISI- Matsuda: insulin sensitivity index proposed by Matsuda and DeFronzo; Hs- CRP: high sensitivity C-reactive protein.

fat mass percentage, fat mass index, trunk fat mass than their nonsarcopenic obese counterparts ($p < 0.05$). Moreover, absolute fat-free mass, fat-free mass percentage, fat- free mass index, appendicular skeletal muscle mass and appendicular skeletal muscle index (ASMM/ h^2) were significantly lower in sarcopenic obese subjects than nonsarcopenic obese individuals ($p < 0.05$).

From a metabolic point of view, HOMA- IR was significantly higher and ISI- Matsuda significantly lower in sarcopenic obese subjects than nonsarcopenic obese subjects ($p < 0.05$), independently of gender.

Data about the prevalence of metabolic syndrome and of its single components are presented in Table 2. The presence of metabolic syndrome was significantly higher in sarcopenic obese subjects when compared to nonsarcopenic obese subjects (47.6% versus 34.3%, $p< 0.001$). Even when considered singly, criteria for the diagnosis of metabolic syndrome were more prevalent in sarcopenic obese subjects than nonsarcopenic obese individuals (Table 2).

In addition, the mean value of ASM/ weight was significantly decreased in subjects with metabolic syndrome when compared to their counterparts without metabolic syndrome (whole sample: 0.2522±0.0410 vs 0.2423±0.0352, p=0.001;males: 0.2946±0.0289 vs 0.2808±0.0311, p=0.026; females: 0.2385±0.0298 vs 0.2297±0.0255, $p< 0.001$).

Moreover, albumin levels were significantly decreased, and hs- CRP levels were significantly increased in sarcopenic obese subjects, in both men and women, when compared to their nonsarcopenic obese counterparts (see Table 1 for p values).

Discussion

In the present study we showed that significant differences emerged between sarcopenic obese adult subjects and their nonsarcopenic obese counterparts from the metabolic and inflammatory point of view, using a definition of sarcopenic obesity based on the ASMM/ weight ratio and BMI ≥ 30 kg/ m^2.

With respect to body composition and the metabolic profile, our findings are consistent with previous studies (11, 15, 30),

Table 2
Prevalence of metabolic syndrome and sarcopenic obesity

		Sarcopenic obese subjects N= 418	Nonsarcopenic obese subjects N= 309	p
Single components of metabolic syndrome (%)	Abdominal obesity (WC > 102 cm in men; > 88 cm in women)	97.9	84.1	<0.001
	Triglycerides (≥ 150 mg/dl)	29.8	22.0	0.004
	HDL-cholesterol (< 40 mg/dl in men; < 50 mg/dl in women)	48.1	42.8	0.048
	Blood pressure (≥ 130/≥85 mmHg)	39.3	31.8	0.010
	Fasting glucose (≥ 110 mg/dl)	37.2	22.6	<0.001
Number of components of metabolic syndrome (%)	0	1.5	8.6	<0.001
	1	20.8	26.2	
	2	30.1	30.9	
	3	27.7	22.4	
	4	13.9	7.2	
	5	6	4.7	
Metabolic syndrome (%)	≥ 3 risk factors	47.6	34.3	<0.001

Legend: WC= waist circumference.

showing that increased fat mass, especially visceral fat mass, and decreased muscle mass are associated with cardiometabolic abnormalities. In particular, recent studies carried out in Asian ethnic groups (15-17, 19, 30) and, to a lesser extent, in White or White- mixed American cohorts (8, 20), reported a close association between sarcopenic obesity and metabolic syndrome.

An advantage in our study is represented by the fact that we performed an oral glucose tolerance tests in order to calculate the ISI- Matsuda index, assessing more thoroughly the impairment of insulin sensitivity, with respect to previous analogous studies, in which insulin resistance was expressed using HOMA- IR (just considering fasting glucose and insulin levels) (31). Anyway, in our study population, results in terms of ISI- Matsuda were consistent with findings in terms of HOMA- IR, confirming a significantly worst insulin sensitivity in sarcopenic obese subjects than nonsarcopenic obese individuals.

In our sample of sarcopenic obese subjects, hs- CRP levels were higher than nonsarcopenic obese subjects, indicating the presence of a more pronounced low- grade inflammatory status accompanying the phenotype of sarcopenic obesity than obesity without sarcopenia. Likewise, inflammation was shown to be higher in sarcopenic obese subjects than nonsarcopenic obese individuals of mixed ethnicity (8, 32, 33). In a paper by Cesari et al., it was demonstrated that proinflammatory cytokines, as well as C-reactive protein, are positively associated to adipose tissue and negatively related to muscle mass (34). In addition, accumulating evidence suggested that obesity and sarcopenia may act synergistically through the mechanisms of insulin resistance and inflammation; in particular, chronic low- grade inflammation is known to play a crucial role in the mechanism of the obesity- related insulin resistance (32-35). In fact, impairment of insulin sensitivity and the inflammatory status represent the common soil for changes in body composition (fat mass accumulation and lean mass decline) as well as for the metabolic aspects (especially the development of metabolic syndrome) (2, 11).

Decline in muscle mass typically occurs during aging, with a peak after the age of 60 (2); actually, this process already starts after the third decade, and can be exacerbated by sedentariness, often linked to obesity (2, 37). The majority of the extant studies dealing with sarcopenic obesity was performed in older adults or included both pregeriatric and geriatric study groups (16-21, 36, 38). In our study, we selected an adult population in order to minimize effects of body composition changes in late life.

Even if comparison of our results with previous findings is limited, due to the use of different definitions of sarcopenia and obesity (10, 12), as well as to differences in terms of ethnicity in the existing studies (16-21), some conceptual observations could be useful.

Our results are in line with findings in prior studies (15, 16, 36, 39) in which the use of a definition based on ASMM/ height squared tended to underestimate the prevalence of sarcopenia in obese subjects. Similarly, in a study by Newman and coll. (39), it was observed that none of the obese elderly subjects satisfied the ASMM/ h^2 criterion for sarcopenia. Zamboni

et al. (36) argued that absolute lean mass, even though not decreased, may not be sufficient for such an increased body size in obese individuals. In other words, correcting skeletal muscle for body mass or fat mass may be more exhaustive in describing the discrepancy in body compartments, leading to a better classification of sarcopenic obese subjects not only from a functional, but also metabolic point of view. In our study, the low number of subjects classified as sarcopenic basing on the cutoffs of ASMM/ h^2 prevented the statistical analysis comparing sarcopenic obese subjects according to the two different indices used.

The finding of lower albumin levels in sarcopenic obese subjects in our study may be explained, at least in part, by the level of inflammation, that is known to negatively affect albumin concentrations (40); moreover, a negative association between albumin and skeletal muscle mass was found in older adults (40). Insulin resistance has been postulated and recognized to play an important role on aging muscle, as reduced anabolic action of insulin on protein metabolism is one of the main causes leading to lean body protein mass decline (41, 42). The onset of insulin resistance, as it occurs in case of excess fat mass, could be detrimental in terms of protein metabolism also in early stages of aging in young adult life (43).

In previous studies about sarcopenic obesity, scarce attention was directed to protein and albumin status (16-21, 36); our observations suggest that this aspect should be further explored also in young adult and pregeriatric adult subjects in such a condition of mixed malnutrition that is sarcopenic obesity (over- nutrition as excess fat mass and under- nutrition as low muscle mass), using more precise markers of protein metabolism than albumin (43).

Our study has several limitations. Hormonal changes, in particular variations in sexual hormones, are known to influence body composition alterations during the aging process (44, 45); in our study, we did not perform a separate analysis of sarcopenic obese and nonsarcopenic obese women according with the menopausal state, and we did not consider hormonal status in both genders. Another limitation to our paper is the use of the BMI to define obesity: even if BMI has been widely used in the literature to detect obesity, it is not able to distinguish body components (46). On the other hand, body composition was assessed using DXA, that is more accurate than BMI but some shortcomings have been reported when evaluating body compartments in obese subjects, especially in terms of underestimation of abdominal fat mass and overestimation of thigh muscle mass (47).

Conclusion

The phenotype of sarcopenic obesity is characterized by body composition changes that are associated with metabolic derangements, mainly affecting cardiometabolic risk. Even though preliminary research on sarcopenic obesity was addressed to functional consequences in elderly subjects, more recent findings- including the present study- suggest that metabolic aspects linked to sarcopenic obesity may appear in the early stages of the aging process, before the onset of physical performance impairment. Noteworthy, in sarcopenic obese subjects insulin resistance may act not only per se as a risk factor for cardiometabolic sequelae but it may represent an additional factor accelerating age- related muscle mass decline, by interfering with protein metabolism. Thus, further research should be prompted in order to explore more clearly the connections between the phenotype of sarcopenic obesity and its clinical and metabolic implications. Finally, a greater awareness is needed towards the constellation of the abovementioned aspects of sarcopenic obesity also in young adult subjects, in order to prevent the development of clinical and functional impairment in late life.

Conflict of Interest: The authors have nothing to disclose

Ethical Standards: The study protocol was approved by the Ethical Committee of the «Sapienza" University of Rome, and written informed consent was obtained from all the participants.

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