



Revisión

Association between sarcopenic obesity and cardiovascular risk: where are we? *Asociación entre obesidad sarcopénica y riesgo cardiovascular: ¿dónde estamos?*

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Abstract

Introduction: The main changes in the body composition refer to the increase of adipose tissue and/or the decrease of muscular mass, and these changes have effect in many clinical outcomes. Sarcopenic obesity (SO) consists of the presence of excessive adipose tissue and deficit of muscular mass simultaneously. People with SO may have synergistic effect due to obesity and sarcopenia, with increases cardiovascular risk more than obesity itself.

Objective: To describe the findings in the literature about the association between SO and risk factors and/or cardiometabolic disease (CMD) or cardiovascular disease (CVD).

Methods: An electronic search was done on the following databases: MEDLINE, Scopus, SciELO, LILACS and Web of Science, using the matching expressions and Boolean operators: "obesity sarcopenic" OR "sarcopenic obesity", in the titles of the studies, AND "cardiometabolic disease" OR "cardiovascular disease" OR "metabolic syndrome" OR "insulin resistance", in the abstract.

Results: Most of studies are cross-sectional and present many different diagnosis criteria for SO. It was possible to verify the association of the SO and the risk factors and/or CMD or CVD.

Conclusion: SO is associated with risk factors and/or CMD or CVD. The lack of a consensus about this definition jeopardizes the effective clinical practice and the research about the subject.

Key words:

Obesity. Sarcopenia. Sarcopenic obesity. Cardiometabolic disease. Cardiovascular disease.

Resumen

Introducción: los principales cambios en la composición del cuerpo refieren el incremento de tejido adiposo y/o la disminución de masa muscular, y estos cambios tienen efecto en varios resultados clínicos. La obesidad sarcopénica (OS) consiste en la presencia simultánea del exceso de tejido adiposo y el déficit de masa muscular. Las personas con OS pueden tener un efecto sinérgico debido a la obesidad y la sarcopenia, lo que incrementa el riesgo de enfermedad cardiovascular, más que la obesidad en sí.

Objetivo: describir los hallazgos en la literatura científica sobre la asociación de la SO y los factores de riesgo y/o ECM (enfermedad cardiometabólica) o enfermedad cardiovascular (ECV).

Métodos: se realizó una búsqueda electrónica en las siguientes bases de datos: MEDLINE, Scopus, SciELO, LILACS y Web of Science, usando las expresiones coincidentes y los operadores booleanos: "obesidad sarcopénica" o "sarcopénica obesidad", en los títulos de los estudios, y "enfermedad cardiometabólica" o "enfermedad cardiovascular" o "síndrome metabólico" o "resistencia a la insulina", en el *abstract*.

Resultados: la mayoría de los estudios son de corte transversales y presentan diferentes criterios de diagnóstico para la OS. Fue posible verificar la asociación de la OS y los factores de riesgo y/o ECM o ECV.

Conclusión: la OS está asociada con los factores de riesgo y/o ECM o ECV. La falta de un consenso sobre esta definición pone en peligro la efectividad de la práctica clínica y la investigación sobre el tema.

Palabras clave:

Obesidad. Sarcopenia. Obesidad sarcopénica. Enfermedad cardiometabólica. Enfermedad cardiovascular.

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INTRODUCTION

The assessment of body composition (BC) allows the measuring of larger body compartments such as fat-free mass which also includes the bone mineral tissue, body fat mass and total body water (1). The use of this evaluation has grown due to the increase in the prevalence of chronic diseases, overweight and obesity worldwide and it has been used to assess adverse health outcomes in conditions of BC changes (1,2).

The main changes of BC are related to excess of adipose tissue (AT) and/or the deficit of muscular mass (MM), defined as obesity, sarcopenia or sarcopenic obesity (SO), when both conditions appear simultaneously (1). The prevalence of SO has increased in industrialized countries due to the high number of cases of obesity and sarcopenia in obese people, ranging from 4.4% to 42.9%, depending on the diagnostic methods and on the studied population (3-21). There is not a consensus between the definition and classification of SO, and this gap contributes to the inconsistent findings in its association with clinical outcomes (22-24).

Knowledge about the consequences of the SO to health were initially limited to functional outcomes. Recently, the associations between this condition and cardiometabolic disease (CMD), cardiovascular disease (CVD) and mortality has been the target of growing attention (12,22,25), justifying the study of these relationship since SO can be prevented or treated.

OBJECTIVE

The objective of this review is to describe the findings in literature about the association between SO and the risk factors and/or CMD or CVD.

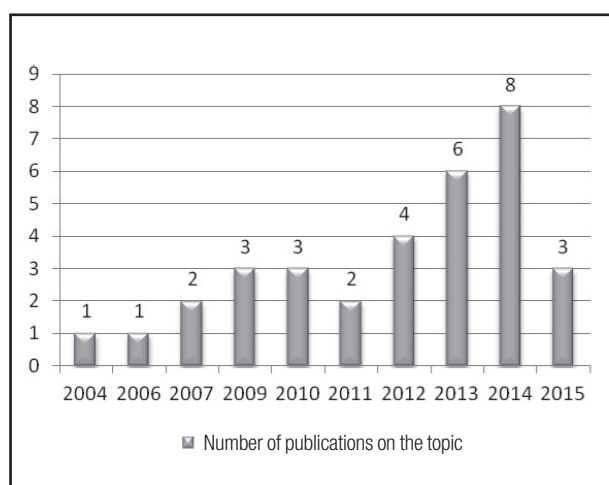


Figure 1.

Evolution of the number of publications on the topic; association between sarcopenic obesity and risk factors and/or CMD or CVD.

METHOD

Review of the literature in English, Spanish and Portuguese, indexed in MEDLINE, Scopus, SciELO, LILACS and Web of Science. No filter of date were used. Combinations of Boolean operators and descriptors used were: "obesity sarcopenic" OR "sarcopenic obesity" in the title of the work AND "cardiometabolic disease" OR "cardiovascular disease" OR "metabolic syndrome" OR "insulin resistance" in the abstract. The last search was held on September, 2015. The articles were selected by their titles and abstracts and a detailed analysis was done with the full articles. Search included cross-sectional, prospective or retrospective studies with adults (> 18 years) and elderly.

RESULTS

Although described in the literature for a long time, the first studies linking SO to CMD and/or CVD and their risk factors (Fig. 1) date from 2004 and the number of publications is growing every year including those that discuss the association of SO with risk factors and/or CMD and CVD in people with different clinical conditions (Fig. 2).

Thirty-nine articles were identified, but only 33 were related to the objective of this study. It is noteworthy that most studies are cross sectional. Table I shows the studies found on the association between OS and risk factors and/or CMD and CVD. In addition 24 references were included because of its relevance in the theoretical basis of this study.

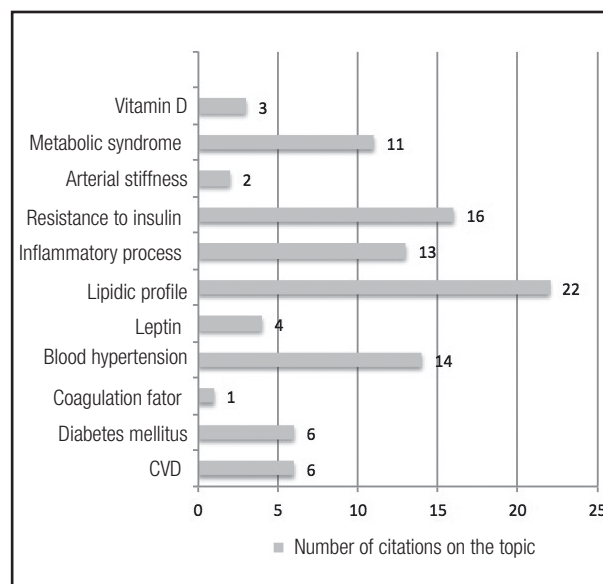


Figure 2.

Review of risk factors and/or CMD and CVD that had been evaluated in the cited publications.

Table I. Review of the studies that investigate the association between sarcopenic obesity and risk factors and/or cardiometabolic and cardiovascular diseases in adults and elderlies

Author, year study design	Characteristics of the population	Mensuration of SO	Risk or cardiometabolic / cardiovascular diseases	Main findings
Baumgartner et al., 2004 (4) Cross-sectional	n = 451 (M/W) Age ≥ 60 y	DXA (SC = ASM/height ² ; OB = %FM)	MetS	The prevalence of MetS was higher in patients with OS (19.2%) compared to healthy and sarcopenic groups
Auberlin et al., 2006 (35) Cross-sectional	n = 22 (W) Age: 55-75 y	DXA (SC = SMI/height (m ²); OB = %FM)	Lipid profile; glycemia; HOMA-IR; CRP	Obesity without sarcopenia, is associated with changes in lipid profile, even after adjusting the variable visceral fat
Schrager et al., 2007 (38) Cross-sectional	n = 871 (M/W) Age ≥ 65 y	SC = HS ≤ 19 kg (W) and ≤ 33 kg (M); Anthropometry (OB = BMI ≥ 30 kg/m ² or WC ≥ 98 cm)	Inflammatory markers (CRP; IL-6; soluble receptor IL6, TNF-alpha, IL-18 and antagonist receptor of IL-1)	SO (WC ≥ 98 cm), was associated with elevated levels of IL-6 (F = 4.58, p = 0.033) and IL-6 soluble receptor (F = 6.24, p = 0.013)
Honda et al., 2007 (55) Prospective cohort	n = 328 (M/W) Age: 53 ± 12 y	SC = Global subjective assessment; Anthropometry (OB = BMI > 25 kg/m ²)	Inflammatory markers (CRP, IL-6; TNF-alpha); Leptin	Individuals with SO showed higher prevalence of diabetes and higher levels of leptin CRP and IL-6
Stephen & Janssen, 2009 (5) Prospective cohort	n = 3,366 (M/W) Age ≥ 65 y	BIA (SC = muscle mass adjusted by height); HS (SC = HS adjusted by height); Anthropometry (OB = WC)	Coronary cardiac disease; congestive cardiac failure; cerebrovascular accident	The rate of coronary events in sarcopenic obese increased 23% (BIA) and in 33% (HS). The risk of congestive cardiac failure in individuals with SO, considering BIA was 42% higher
Messier et al., 2009 (46) Cross-sectional	n = 136 women in post menopause	DXA (SC = ASM/height); Anthropometry (OB = BMI)	Lipid profile; inflammatory markers; insulin sensitivity	Individuals with SO did not show unfavorable metabolic profile when compared to obese individuals
Kim et al., 2009 Cross-sectional (6)	n = 526 (M/W) Age ≥ 20 y	DXA (SC = SMI; OB = %FM)	MetS	Individuals with SO had a higher prevalence of MetS (55.6%) and higher number of risk factors for MetS
Lim et al., 2010 (33) Cross-sectional	n = 284 (M/W) Age: 20-88 y	CT (SO = reason area of visceral fat / muscle area of quadriceps (VMR))	MetS	Individuals with higher VMR had a higher prevalence of MetS. The VMR was positively correlated with the number of components of MetS
Lim et al., 2010 (7) Cross-sectional	n = 565 (M/W) Age ≥ 65 y	DXA (SC = ASM/ height ² e ASM/body mass in kg); CT (OB = VFA > 100 cm ²)	MetS (WC ≥ 90 cm in men ≥ 80 cm in women); HOMA-IR	SO (ASM/ HT ²) was associated with higher (HOMA-IR) and higher levels of TGL. The SO group had 8.2 times higher risk of MetS than normal individuals
Srikanthan et al., 2010 (40) Cross-sectional	n = 14,528 (M/W) Age > 20 y	BIA (SC = SMI); anthropometry (OB = BMI > 30 kg/m ²)	Insulin resistance (HOMA-IR); dysglycemia (HbA1Cg); pre-diabetes (HbA1Cg and fasting glucose); diabetes (HbA1Cg and fasting glucose)	Individuals with SO had the stronger associations with insulin resistance, dysglycemia, pre-diabetes and diabetes

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Author, year study design	Characteristics of the population	Mensuration of SO	Risk or cardiometabolic / cardiovascular diseases	Main findings
Kohara et al., 2011 (3) Cross-sectional	n = 782 (M/W) elderlies	CT (SC = sectional area of the muscle of thigh adjusted by body mass; OB = VFA >100 cm ²)	Leptin; lipid profile; BP; fasting glucose; serum level of insulin; HbA1Cg; HOMA-IR	Individuals with SO have higher levels of leptin, fasting plasma glucose, serum insulin, HbA1C, HOMA-IR and total lymphocytes count
Kim et al., 2011 (23) Cross-sectional	n = 526 (M/W) Age: 53.6 ± 15.6 y	DXA; TC SO = Index ASM/height ² /VFA	MetS; arterial stiffness	The lowest tertile of the index presented OR of 5.43 95% IC 2.56-13.34) for MetS. As the index is an independent determinant of arterial stiffness
Kohara et al., 2012 (50) Cross-sectional	n = 1,024 (M/W) Adults and elderlies	CT (SC = transversal area of femoral muscle/weight in kg; OB = VFA > 100 cm ²)	Arterial stiffness = velocity of pulse brachial ankle	Individuals with SO had higher arterial stiffness values than the control, only in men
Levine & Crimmins, 2012 (8) Cross-sectional	n = 1,127 (M/W) Age ≥ 60 y	DEXA (SC = Skeletal muscle mass); anthropometry (OB = WC)	HOMA-IR; CRP	The group of individuals with SO have higher levels of CRP
Levine & Crimmins, 2012 (9) Cross-sectional	n = 2,287 (M/W) Age ≥ 60 y	DEXA (SC = ASM/body mass in kg x 100); anthropometry (OB = WC)	HOMA-IR; CRP	Sarcopenic obese individuals had higher insulin resistance index
Hwang et al., 2012 (10) Cross-sectional	n = 2,221 (M/W) Age ≥ 60 y	DXA (SC = ASM/body mass in kg x 100); anthropometry (OB = WC)	HbA1C; fasting glucose; insulin; lipid profile; PTH; serum vitamin D	Serum insulin levels and vitamin D were associated with SO in both sexes. Serum glucose and TGL levels were associated SO in women and PTH levels increased the risk of SO in men
Park et al., 2013 (49) Cross-sectional	n = 6,832 (M/W) Adults	DEXA (SC = ASM/body mass in kg); anthropometry (OB = WC)	BP	Compared with healthy subjects, patients with SO have 6 times more likely to have BP
Chin et al., 2013 (43) Cross-sectional	n = 1,578 (M/W) Age ≥ 65 y	DEXA (SC = ASM/body mass in kg); anthropometry (OB = BMI)	Lipid profile; HOMA-IR; prevalence of DM; prevalence of CVD	Individuals with SO had higher levels of TGL and HOMA-IR. SO not associated with CVD
Kim et al., 2013 (11) Cross-sectional	n = 493 (M/W) Age ≥ 20 y	DXA (SC = SMM); CT (SO = VFA > 100 cm ²)	HOMA-IR; CRP; vitamin D; MetS	SO was associated with HOMA-IR in both sexes, vitamin D in men and CRP in women
Kim et al., 2013 (12) Cross-sectional	n = 298 (M/W) Age: 20-70 y	DXA (SC = ASM/body mass in kg x 100); CT (OB = VFA > 100 cm ²)	Serum levels of A-FABP; systolic and diastolic BP; lipid profile; fasting glucose; levels of insulin; HOMA-IR; serum leptin; CRP; IL- 6; TNF-α	The group with SO showed higher BP, total cholesterol, TGL, HOMA-IR, levels of CRP, IL-6, leptin and A-FABP levels, in both sexes. Women with SO had higher BP systolic and TGL and lower HDL levels

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Table I. Review of the studies that investigate the association between sarcopenic obesity and risk factors and/or cardiometabolic and cardiovascular diseases in adults and elderlies

Author, year study design	Characteristics of the population	Mensuration of SO	Risk or cardiometabolic / cardiovascular diseases	Main findings
Lu et al., 2013 (13) Cross-sectional	n = 600 (M/W) Age: 63.6 ± 10.1 y	BIA (SC = SMI); anthropometry (OB = BMI)	MetS	The group of individuals with SO demonstrated higher odds ratio for MetS (OR 11.59, 95%CI 6.72-19.98)
Chung et al., 2013 (14) Cross-sectional	n = 2,943 (M/W) Age ≥ 60 y	DXA (SC = ASM adjusted by body mass); anthropometry (OB = BMI > 25 kg/m ²)	BP; HOMA-IR; lipid profile; inflammatory markers; levels of vitamin D; hepatic function; renal function; ferritin; leukocytes; MetS	The prevalence of MetS and Vitamin D deficiency was higher in patients with SO. HOMA-IR, levels of TGL, ferritin and leukocytes were higher in the group with the SO, as well as vitamin D levels were lower in this group
Baek et al., 2014 (15) Cross-sectional	n = 3,483 (M/W) Age ≥ 65 y	DXA (SC = ASM adjusted by the body mass and height); anthropometry (OB = BMI ≥ 25 kg/m ²)	Lipid profiles; MetS; HOMA-IR	Men with SO have higher OR for dyslipidemia and rising of TC, TGL, LDL and relative TGL/HDL and decreased HDL
Liu et al., 2014 (16) Prospective cohort	n = 680 (M) Age ≥ 75 y old	HS (SC = HS < 22.5 kg); anthropometry (OB = WC ≥ 90 cm)	BP; lipid profile; fasting glucose; MetS; risk of mortality	The group of individuals with SO have a higher prevalence of diabetes mellitus and lower HDL levels
Dos santos et al., 2014 (17) Cross-sectional	n = 149 (W) Average age: 67.1 ± 6.12 y	DXA (SC = ASM; OB = FM) SO = residual value of equation that predicts ASM based on the height and fat mass)	BP; lipid profile; HOMA-IR; CRP	There was no significant difference in blood pressure, blood glucose, HOMA-IR, lipid profile and inflammatory pattern between the group with SO and other groups
Atkins et al., 2014 (47) Prospective cohort	n = 4,252 (M) Age: 60-79 y	Anthropometry (SC = mid-arm circumference; OB = WC > 102 cm)	Mortality in general and because of cardiovascular disease; Cardiovascular events; Events of coronary disease	There was not an association between body composition and other evaluated factors. Individuals with OS had higher levels of PCR
Ohara et al., 2014 (51) Cross-sectional	n = 1,470 (M/W) Adults and elderlies	CT (SC = transversal sectional area of the thigh; OB = VFA > 100 cm ²)	Arterial stiffness: speed of brachial pulse ankle	SO was significantly associated with arterial stiffness
Han et al., 2014 (44) Cross-sectional	n = 4,846 (M/W) Age ≥ 60 y	DXA (SC = ASM/ body mass in kg) and anthropometry (OB = BMI ≥ 25 kg/m ²)	BP; lipid profile; insulin resistance; evaluation of previous CVD	Individuals with SO presented 3 times more chances of showing high blood pressure. The group with SO showed higher percentage of individuals with previous high BP, using anti-hypertensive and with previous CVD and higher levels of TGL and HOMA-IR
Park et al., 2014 (45) Cross-sectional	n = 6,832(M/W) Age ≥ 19 y	DXA (SC = ASM/ body mass in kg); anthropometry (OB = WC)	MetS	SO was associated to the increase for MetS in men and women
Kim et al., 2014 (19) Cross-sectional	n = 298 (M/W) Age: 20-70 y	DXA (SC = SMI); CT (OB = VFA ≥ 100 cm ²)	Cardiorespiratory fitness; BP; lipid profile; HOMA-IR; leptin; IL-6; CRP	The group SO presented lower cardiorespiratory fitness, higher levels of TGL, leptin and BP and lower HDL levels

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Author, year study design	Characteristics of the population	Mensuration of SO	Risk or cardiometabolic / cardiovascular diseases	Main findings
Yang et al., 2015 (20) Cross-sectional	n = 844 (M/W) Age ≥ 65 y	DXA (SC = SMI; OB = % FM)	Inflammatory process: CRP, IL-6 and TNF- α	SO is associated with the increase of CRP levels, in men
Kim et al., 2015 (21) Cross-sectional	n = 3,320 (M/W) Age ≥ 40 y	DXA (SC = ASM/body mass kg); anthropometry (OB = BMI ≥ 25 kg/m ²)	Framingham Risk Score	The prevalence of risk ≥ 20% for risk of CVD in 10 years was higher in the group of sarcopenic obese, reaching 26.8%
Choudhary et al., 2015 (54) Prospective cohort	n = 82 (M/W) Average age: 50.5 ± 10.65 y	BIA (SC = muscle mass); Anthropometry (OB = BMI > 25 km/m ²)	MetS	SO individuals with MetS had higher percentages as well as greater number of positive components syndrome

A-FABP: adipocyte fatty acid-binding protein; ASM: appendicular skeletal muscle mass; AT: adipose tissue; BIA: bioelectric impedance analysis; BMI: body mass index; BP: blood pressure; CRP: C-reactive protein; CT: computerized tomography; CVD: cardiovascular disease; DM: diabetes mellitus; DXA: dual energy X-ray absorptiometry; FM: fat mass; HDL-C: high-density lipoprotein; HOMA-IR: homeostatic model assessment insulin resistance; HS: handgrip strength; IL-6: interleukin 6; LDL: low-density lipoprotein; M: man; MetS: metabolic syndrome; OB: obesity; PTH: parathyroid hormone; SC: sarcopenia; SMI: skeletal muscle mass index; SO: sarcopenic obesity; TC: total cholesterol; TGL: triglycerides; VFA: visceral fat area; W: woman; WC: waist circumference; y: year.

These papers were presented and discussed in four sessions:

1. SO (definition, diagnosis and physiopathology);
2. OS and risk factors for cardiometabolic and cardiovascular disease;
3. SO, cardiometabolic and cardiovascular disease.
4. SO, CVD and CMD in special clinical situations.

Session 2, 3 and 4 shows the 33 selected works. Six articles were excluded due to language or do not meet the objectives of this study.

SARCOPENIC OBESITY (DEFINITION, DIAGNOSIS AND PHYSIOPATHOLOGY)

The term SO was first described by Baumgartner et al., and was defined by the combination of sarcopenia and obesity (25,26). The heterogeneity of the definitions of SO in the studies may interfere in the results and can be categorized in seven aspects that involve: the method of analysis of BC used, the cutoff point for sarcopenia and obesity classification, the adjustment of MM by body mass or height of the individual, the compliance of the method, the study design, the biologic validity and the predictive risk (2). All these categories are important for a standard definition of SO, but the adjustment of the amount of MM seems to have a higher impact in the discrepancies found in the associations between SO and CMD or CVD (22).

Measurement methods as computed tomography (CT), DEXA (dual X-ray absorptiometry) and the BIA (Bioelectrical Impedance Analysis) have been used to assess the total or skeletal MM (25). Many definitions of sarcopenia have been proposed, but so far none has been universally adopted. Baumgartner et al., 1998 (27) defined sarcopenia as the condition of an individual which the appendicular skeletal muscle mass (ASM) divided by the square of height (ASM/h²) is two standard deviations (SD) below of the average of young population of reference. However, this index is highly correlated with body mass index (BMI) and it classifies individuals with low BMI as sarcopenic and could subestimate the sarcopenia in individuals who are overweight and obese (28). Janssen et al. (29), in turn, in 2002 proposed a definition of sarcopenia with the skeletal mass index (SMI) by the skeletal MM divided by body mass of the subject, both in kilograms and multiplied by 100 [(MM/body mass)x100], so that individuals were considered to have a normal SMI if their SMI was greater than one SD above the sex-specific mean for young adults (aged 18-39). ASM adjusted by the body mass has been described as the most appropriate index to identify sarcopenia (5,7,15). A definition of sarcopenia was proposed by The European Working Group on Sarcopenia in Older People, in 2010, and suggests consider for diagnosing sarcopenia, not only the amount of MM but the presence of both changes, deficit of MM and low muscle function (25,30), but this criterion was not used in the studies found.

Independently of the BC analysis, a complex etiology is associated with the development of SO. It can occur in elderly, in sedentary adults with body weight gain or in obese adults with chronic comorbidities with active inflammatory process (2,31).

Many explanations for SO have been proposed and evidences suggest that a vicious cycle between the accumulation of AT and the deficit of MM is responsible for keeping the development of the phenotype (22).

The increase of AT, especially visceral fat, as well as the excess of free fatty acids may induce chronic inflammation by increased secretion of pro-inflammatory cytokines such as TNF- α and interleukin-6 (15,22). The inflammatory process, in turn, not only causes degradation of MM but also promotes insulin resistance (15) that contributes to the changes in the morphology, size and muscle function, leading to the onset and progression of sarcopenia (22,32).

The skeletal muscle is an important tissue to capture glucose and its decrease may promote insulin resistance and its consequences (31,33,34). Sarcopenia increases insulin resistance, reduces energy expenditure and physical activity, which in turn may lead to an increase of AT, particularly of visceral fat, perpetuating the process (6,22).

Histologically, the SO presents itself as type II muscle fiber atrophy and an infiltration by adipocytes and lipids deposition on the muscular tissue, limiting its metabolic and endocrine action (22,35). To explain this characteristic, it has been suggested that muscle satellite cells *in vitro* have the ability to form adipocytes and myocytes. In human, in some pathologic situations as obesity, hyperglycemia, in the presence of high plasmatic concentrations of fatty acids, as well as the presence of physical inactivity, these satellite cells can acquire adipocytes characteristics, which would explain the presence of mature adipocytes in the muscle tissue (22). They have suggested that intramyocellular triglycerides (IMTG) are an important factor associated with inflammatory process and insulin resistance in the skeletal muscle as long chain fatty acids, diacylglycerol, and ceramides (22).

A metabolic pathway that plays a key role in regulating energy metabolism in muscle tissue is the AMP-activated protein kinase pathway. The activation of this pathway leads to the reduction of IMTG and decreases the syntheses of other factors which may induce the inflammatory process and insulin resistance. The dysregulation of this pathway occurs in certain circumstances as aging or some illnesses as obesity, metabolic syndrome (MetS) and CVD and it can contribute to fat accumulation, inflammation and insulin resistance. These facts contribute to maintain the phenotype (22) and that is why some studies indicate insulin resistance as a path for the understanding the SO (36) as in the study MrOS which administration of an insulin sensitizer in diabetic patients significantly reduced the decline in free fat mass when compared to healthy controls (37).

Inflammation also plays a central role in the pathogenesis of insulin resistance and its presence in both changes in BC: obesity and sarcopenia (38,39). In obesity, the accumulation of intramyocellular lipids results in a bioactive lipid intermediates and lipids peroxides that activate the inflammatory cascade (32,40). Furthermore, similar to the AT, muscle tissue has recently been considered an endocrine organ secreting hormones that modulate systemic metabolism. Analogs adipokines, myokines are responsible for inhibiting and preventing inflammation and insulin resistance. In

individuals with SO the relative scarcity of myokines compared to adipokines increase the risk of CVD and CMD (32,40).

A new adipokine, A-FABP (adipocyte fatty acid-binding protein), has been described as a link between obesity, inflammatory process and insulin resistance and may be involved in the pathogenesis of SO (12). It is predominantly expressed in the adipocyte and macrophage and a significant portion is released in the bloodstream. It binds to fatty acids with high affinity, and acts in the transportation of intracellular fatty acids, in the regulation of the lipid metabolism and in the modulation of gene expression. It is possible that A-FABP works as a lipid hormone transporter or in an hormone-like fashion to modulate the systemic insulin sensibility and the energy metabolism. Some studies show that A-FABP are positively associated to body fat and negatively to MM and in human, it is associated with severity of insulin resistance and its consequences (12).

Besides the inflammatory process and insulin resistance, leptin is highlighted in the physiopathology of SO. It is secreted by adipocytes and has physiologic and physiopathologic actions in several organs, including skeletal muscle where it acts stimulating lipolysis and insulin sensitivity (3,32). The leptin receptors have been shown to be negatively regulated by leptin itself and by insulin resistance. In obese subjects, serum leptin levels increase with fat deposition diminishing its beneficial effect in skeletal muscle (3). Studies show that individuals with SO have higher serum leptin levels when compared to obese, sarcopenic or control groups (3,12,19). Serum leptin levels also correlated negatively with the MM indicators and positively with the AT indicators (3,19).

The vicious cycle between the accumulation of AT and the loss of MM can be associated with CMD and/or CVD via a large network of factors including mainly pro inflammatory cytokines and insulin resistance, but also oxidative stress, mitochondrial dysfunction, energy intake, physical inactivity and other factors which are identified (22,41,42).

SO AND RISK FACTORS FOR CARDIOMETABOLIC AND CARDIOVASCULAR DISEASES

The studies that investigated the association of OS with known cardiometabolic and/or cardiovascular risk factors, described controversial results depending on the assessed population and the method used for diagnosing OS.

The association between SO and lipid profile was the issue most studied in this review, being present in 22 citations, but it was not the main objective of these studies which limits the conclusions about their results. Only Baek et al. (15), in 2014, investigated the association between SO and dyslipidemia as the principal aim of the study in 3,483 Korean elderly. They defined sarcopenia by ASM adjusted for body mass and obesity by BMI ≥ 25 kg/m². After adjusting for confounding factors the group with SO showed a higher chance of dyslipidemia (OR, 2.82; 95% CI, 1.76-4.51) regardless of sex (15).

Many cross-sectional studies in the Korean population, especially in elderly subjects (7,10,14,43,44), but also in adults (11,12,45), showed that SO was associated with changes in the lipid profile characterized by elevated levels of triglycerides (TGL) (7,10,14,22,43-45), total cholesterol (TC) (22) and reduction of the high density lipoprotein (HDL) (10,11). They used as criterion for diagnosis of sarcopenia, ASM adjusted for body mass and for obesity, BMI > 25 kg/m², the visceral fat area (VFA) by computed tomography (CT) or waist circumference (WC).

When ASM/height (2) was used for evaluation of sarcopenia in this population, an association was identified between SO and increased on the low density lipoprotein (LDL) ($p = 0.032$) (6). Other methods for SO defining how the SMI by DEXA associated with VFA (11,19) and MM Index (SMI) by BIA and BMI (≥ 25 kg/m²) (13) also demonstrated associations between SO and increase of TC (13) and TGL (11,13,19) and reduced HDL (11,19). The use of *handgrip strength* (HS) (16) for defining sarcopenia and visceral fat rate/MM thigh relationships (33) or regard MM skeletal/visceral fat also demonstrated an association between SO and elevation of TGL (23,33), TC (23), LDL (23) and low HDL (16,23,33). Only few studies did not highlighted the association between SO with some changes in lipid profile, but they did not focus on the Korean population, and mostly showed changes in lipid profile related only to obese individuals (3,17,20,21,35,46). It is noteworthy that the studies in Asian populations, mostly Koreans, used as criterion for obesity BMI ≥ 25 kg/m², following the cutoff of World Health Organization (WHO). The use of this cutoff is recommended for international classification, but for public health actions, a lower cutoff BMI is recommended, ≥ 23 kg/m² representing increased risk and ≥ 27.5 kg/m² representing high risk (47). Asians generally have a higher percentage of body fat than white individuals of the same age, sex and BMI representing risk factor for type 2 diabetes and CVD (47,48). This observation lead WHO to debate the proposed methods by which countries could make decisions about the definitions of increased risk for their population (47).

The association between SO and insulin resistance has also been well described in the literature, being cited in 16 of the studies included. Srikanthan et al., 2010 (40), investigated 14,528 healthy individuals aged ≥ 20 years, using BMI > 30 kg/m² for obesity definition and SMI by BIA. Consistent with their hypothesis, the authors showed that the group of individuals with SO had the highest OR for insulin resistance (OR, 2.13; 95% CI, 2.02 to 2.23, $p < 0.0001$), even if excluded diabetic subjects from the analysis (OR, 1.99; 95% CI, 1.89-2.08; $p < 0.0001$). It was also observed that this association was stronger in adults than in elderly (OR, 2.39; 95% CI, 2.24-2.55; $p < 0.0001$ in adults and OR, 1.86; 95% CI, 1.73-2.00; $p < 0.0001$ in elderly) what can be explained by sarcopenia associated with an inflammatory process in these patients, suggesting that inflammation may play a role in the development of metabolic complications of sarcopenia (40). The association between SO and insulin resistance was described, only in women (11), male (12) or in the both sexes (3,7,9,14,15,43,44). All these studies used HOMA-IR (homeostatic model assessment insulin resistance) to investigated insulin

resistance, but different methodologies were used to evaluate sarcopenia: ASM adjusted for body mass (7,11,12,14,15,43,44) or height (9), muscular area in the thigh/visceral fat (3) and the MM index (DEXA) (11) and BMI (12,14,15,43,44), VFA (3,7,11) and WC (9) for evaluate obesity. Individuals with SO showed a higher HOMA-IR when compared to others who were obese, sarcopenic or normal individuals (3,7,9,11,12,14,15,43,44).

Even the HOMA-IR showed a negative correlation with the storage of MM and positive correlation with the AT reserve (19), some studies found higher HOMA-IR values in the group of obese individuals with sarcopenia when compared with those OS, sarcopenic and normal subjects (8,19). Only one study (35) showed no difference between sarcopenic obese group and obese, but it used an equation to estimated visceral fat from body fat, which may limit the defining criterion.

Studies intend to evaluate the association of the SO with inflammatory process, using the ASM adjusted by body mass (12), SMI (8,11,20), HS (38) and arm muscle circumference (49), as markers of sarcopenia and VFA (11), WC (8,38,49), the percentage of body fat by DEXA (20) and BMI (12) to identify obesity, showed that individuals with SO had higher ultra-sensitive C-reactive protein levels (CRP US) in women (8,11,12,20,38,49) and men (8,12,20,38,49) and higher IL-6 (12,38) when compared with obese, sarcopenic or normal individuals; but no association with TNF- α (20) e adiponectin (12). So that individuals with SO has 1.4 more likely to have elevation in CRP levels compared to the standard group (OR, 1.438; 95% CI, 1.139-1.815, $p = 0.002$), even after adjusting for other clinical variables that have influence on the inflammatory process (11).

Schrager et al. in 2007 (38) also highlighted that the distribution of fat mass is an important aspect and central obesity is more pro-inflammatory than global obesity. It was also demonstrated a strong effect of muscle strength in predictive model CRP US and IL-6. With these findings, the group provides evidence that central obesity can adversely affect muscle strength by stimulating the production of pro-inflammatory cytokines and IL-6 pathway stimulation.

CRP US also relate to MM assessed by SMI (DEXA) and the VFA, in isolation, of both sexes (11,19). Studies using a regression equation with appendicular skeletal MM and fat mass (17), overweight and sarcopenic individuals (46), the VFA estimated by formula and SMI (35) and the VFA and the area the cross sectional thigh muscle (3), respectively, for the diagnosis of SO did not show any differences between the inflammatory parameters evaluated in the presence and/or absence of obesity and sarcopenia (3,17,35,46). Already Levine & Crimmins, 2012 (9) showed higher CRP levels in non-obese sarcopenic individuals, and attributed this finding by using an indicator of the amount of MM and not functionality. Vitamin D deficiency is another risk factor for CMD and CVD. It has been associated with insulin resistance and type 2 diabetes as well as obesity. Moreover, vitamin D levels, assessed by serum 25 [OH] D, may have an effect on mass and muscle function (11). A high intake of vitamin D and calcium in rats resulted in reduced accumulation of body fat and increase in lean mass, with a commensurate increase in expression of insulin receptors (50).

Studies using the ASM adjusted for body mass and SMI assessed by DEXA as sarcopenia indicator (10,11,14) and BMI (14), the WC (10) and VFA (11) as obesity indicators showed that individuals with OS have lower levels of 25 [OH] D, compared with sarcopenic, obese or normal individuals (11,14), or when compared with those without sarcopenic obesity (10). Although the levels of 25 [OH] D were positively correlated with the amount of lean body mass in both sexes and negatively correlated with visceral fat in men (11), patients with SO of both sexes had higher levels of vitamin D deficit, compared to the other groups (14). Subjects in the highest quartile of distribution of levels of 25 [OH] D showed protection to SO in both sexes (10).

Among other risk factors studied in literature, Atkins et al., in 2014 (49), evaluated the association between SO and homeostasis indicators, such as the plasma levels of D-dimer and the von Willebrand Factor, showing that patients with SO had higher plasma levels of the two indicators.

SO, CARDIOMETABOLIC AND CARDIOVASCULAR DISEASES

Despite evidence, the association between SO and CMD and CVD itself has been less studied (25). There are few prospective studies to examine this association. Five publications with this design were identified, all the others were cross-sectional studies.

The association with hypertension is the most studied. Studies evaluating sarcopenia by ASM adjusted for body mass (12,14,21,44,45,51) and SMI (19) and obesity by BMI (12,14,21,44), the WC (45,51) and VFA (19) showed that both men and women with SO had higher blood pressure values compared with sarcopenic, obese or normal individuals (12,14,19,21). Individuals with SO also had higher prevalence of (44,45) and a higher odds ratio of developing hypertension compared to normal subjects (44,51). The sarcopenic obese group also had the highest percentage of individuals using antihypertensive drugs (44). Studies using the SMI (13,20) to define sarcopenia and BMI (13) and the fat mass (FM) percentage (20) for definition of obesity, identified the association with hypertension only for the obese group (1,20). Others that used HS (16), regression equations (17) or the SMI adjusted for height (6) to define sarcopenia, showed no difference among the groups (obese, sarcopenic, sarcopenic obesity and normals individuals) (6,16,17).

It is known that blood pressure is directly related to body size in the general population. The association between SO and hypertension, can be traced to sarcopenia being independently associated with hypertension, adding to the risk factors of AT accumulation. The loss of MM represents a decrease in insulin responsive mass, promoting insulin resistance and hypertension (44). The arterial stiffness, a risk factor also evaluated, is an important determinant of high blood pressure and predictor of adverse cardiovascular events (36). Studies using cross-sectional area of the thigh muscle and VFA, measured by CT, for diagnosing SO found that the it is associated with increased arterial stiffness (52,53). Resistance training could be recommended to increase the MM and to

improve the protection against hypertension and arterial stiffness in this population (21).

MetS is also evaluated in several studies. The strong relationship between SO and MetS has been little explored, but it is known that the inflammatory process plays a key role in this respect because it is associated with increased AT and MM deficit and insulin resistance, favoring the altered metabolism (13). Studies using diagnostic sarcopenia ASM adjusted for body mass (7,11,14,45) or the height (4,6) and the SMI by BIA (13) and by DEXA (11), and the obesity diagnosis by percentage of FM (4,6), VFA (7,11), BMI (13,14) and WC (45), showed that individuals with SO had higher prevalence of MetS compared to groups regardless of sex (4,11,14,45) and only when compared to normal subjects (6). The SO also showed an association with components of MetS (13) and the amount of components (6) presented by subjects with the syndrome. The OR for MetS was also higher in the group of subjects with SO than in the other groups (OR, 11.59; 95% CI, 6.72-19.98) suggesting that it also can be considered a major risk factor for MetS in addition to sarcopenia and isolated obesity (6,7). The number of components in MetS was also correlated negatively with SMI and positively with VFA, in both sexes (11).

Studies evaluating the SO through the relationship skeletal MM/visceral fat (23) and the rate visceral fat /thigh muscle (33), also found that individuals with SO had higher prevalence of MetS (33), higher reason to chance to MetS (23,33) and is associated with the components of MetS (33). It was observed that MetS components had a negative correlation with the rate ASM/visceral fat (23) and a positive correlation with the rate of visceral fat/thigh muscle (33). But when the SO was evaluated by handgrip strength associated with WC the higher prevalence of MetS was only in the obese group (16).

The CMD studies also show the association between SO and diabetes mellitus. Studies using the HS and the SMI to define sarcopenia and WC and BMI for definition of obesity, showed that there was a higher prevalence of diabetes mellitus among individuals with SO than among others. In the SO group, there was a higher odds ratio of having pre diabetes (OR, 1.46; 95% CI, 1.12-1.75) expressed by a glycated hemoglobin $\geq 6\%$ and $< 6.5\%$ or a fasting glucose ≥ 100 mg/dL and < 126 mg/dL and diabetes (OR, 2.81; 95% CI, 2.30-3.43), expressed by a glycated hemoglobin $\geq 6.5\%$ or a fasting glucose ≥ 126 mg/dL (16,40).

Because of the aforementioned associations and the importance of risk factors, it is necessary to investigate the relationship between SO and the presence of CVD installed. Study using the ASM adjusted for body mass and BMI to define SO, found that older individuals with this phenotype had higher prevalence of coronary heart disease and higher cardiovascular risk in ≥ 10 years (21). The odds ratio for this risk, even after adjusting for confounding variables such as food intake, exercise and alcohol consumption was greater in sarcopenic obese group for both men (OR, 2.49; 95% CI, 1.53- 4.06) and women (OR, 1; 87; 95% CI, 1.02-3.41) (21).

When evaluating sarcopenia through muscle strength, it was also found that compared to normal body composition, the risk of congestive heart failure has increased to 42% ($p = 0.002$) and

the risk for CVD was increased by 23% ($p = 0.006$) in subjects with SO (5).

Chin et al. in 2013 (43) even using the ASM adjusted for body mass and BMI to define SO in elderly Koreans did not identify difference in the proportion of individuals with CVD. As Atkins et al. in 2014 (49) using for diagnosis of SO, the arm muscle circumference and the WC in a cohort of 11 years, also did not identify any association between SO and coronary heart disease and cardiovascular events. Therefore the difference of methods and study designs may contribute to differences in the results of the associations.

Several mechanisms may explain the relationship between SO and the increase of risk for CVD. Based on all described metabolic changes that the MM deficit promotes is the possibility that the skeletal MM acts as a protective agent against CVD, however it is known that the loss of MM does not occur in isolation but is strongly associated with the parallel increase of AT and this mechanism leads to a vicious cycle that works synergistically may also increase the risk for CVD (21).

SO, CVD AND CMD IN SPECIAL CLINICAL SITUATIONS

The ability to stabilize chronic diseases is a great advance in modern medicine, leading to extended life expectancy in the population. However chronic diseases is associated with metabolic abnormalities and changes in body composition can affect your outcome and increase the demand and the cost of the health system. There is a close relationship between the loss of MM and chronic diseases, so that the term sarcopenia which was originally introduced to define the decline in MM associated with age is now used to indicate loss mass or function muscle related to chronic diseases or low-protein and energy intake (31). The causes of sarcopenia in chronic diseases and cancer include inflammation, physical inactivity, sub-optimal protein intake as well as factors related to age.

The sarcopenia with normal or excess AT can be observed in cancer patients undergoing adjuvant chemotherapy (54) and even more so in patients with chronic kidney disease and chronic obstructive pulmonary disease (55). The SO on these clinical situations can be caused mainly by the high prevalence of obesity in the population in general and the presence of the inflammatory system activation in these clinical conditions (31).

The clinical outcomes of patients with chronic diseases and SO are worse than the obese patients with normal MM (31) and in these situations, the SO can also be associated with CVD and CMD. The evaluation of patients after liver transplantation, has identified a prevalence of 88% of SO and these patients had a higher frequency of MetS compared to transplanted without SO (57% vs. 20%, $p = 0.041$) (56). The evaluation of 328 patients with chronic kidney disease in final stages, using BMI and subjective global assessment for diagnosis of SO, found that this group had higher percentage of diabetic patients, as well as higher serum levels of leptin, CRP US and IL-6 (57).

DISCUSSION

The most important problem in clinical practice and research in SO is the lack of a definition. OS is not only the junction of two pathological conditions, but the additive effect of both. Most of the selected studies are cross-sectional and show great discrepancy in methods, but they indicate the association of the SO with cardiovascular risk factors and/or CVD and CMD. The better understanding about this association is important to prevent these effects in the general population and in those individuals with associated diseases.

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Fe de erratas

En *Nutrición Hospitalaria* 2016;33(Suppl. 3):1-3, aparece el artículo "Conclusions of the II International and IV Spanish Hydration Congress. Toledo, Spain, 2nd-4th December, 2015". Como autores de este figuran Aranceta-Bartrina J, Gil A, Marcos A, Pérez-Rodrigo C, Serra-Majem LL, Varela-Moreiras G, cuando lo correcto es que aparezca la cita de la siguiente manera:

Aranceta-Bartrina J, Gil A, Marcos A, Pérez-Rodrigo C, Serra-Majem LL, Varela-Moreiras G, on behalf of the Scientific Committee, Scientific Secretary and Speakers: Drewnowski A, Palou A, Anadón A, Murray B, Gómez-Candela C, Maffei C, Ramón D, Benton D, Corella D, Alonso-Aperte E, Martínez de Victoria E, O'Neal E, Pfeffer F, Braun H, Lukaski H, Polanco I, Bernal J, González-Alonso J, Ordovás JM, del Coso J, Kenney L, Sardinha LB, Díaz-Rubio M, González-Gross M, Kapsokefalou M, Sawka MN, Millard-Stafford M, Palacios N, Watson P, Riobó P, Urrialde R, Mora-Rodríguez R, Maughan RJ, Ortega RM, Gellert R, Oliver S, Trangmar S and Partearroyo T. Conclusions of the II International and IV Spanish Hydration Congress. Toledo, Spain, 2nd-4th December, 2015. *Nutr Hosp* 2016;33(Suppl. 3):1-3.