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Oxidative stress is increased in sarcopenia and associated with cardiovascular disease risk in sarcopenic obesity

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ABSTRACT

Objectives: To define whether circulating markers of oxidative stress correlate with sarcopenia in terms of glutathione balance and oxidative protein damage, and whether these biomarkers are associated with risk of cardiovascular disease (CVD).

Study design: Population-based cross-sectional study. 115 out of 347 elderly subjects were classified as non-sarcopenic non-obese (NS-NO), sarcopenic non-obese (S-NO), non-sarcopenic obese (NS-O), and sarcopenic obese (S-O).

Main outcome measurements: Sarcopenia was defined as a relative skeletal muscle mass index (RASM) < 7.25 kg/m^2 for men or < 5.67 kg/m^2 for women, while obesity was diagnosed in those presenting with% fat > 27 for men or > 38 for women. The CVD risk was estimated by the carotid intima-media thickness (IMT) and the Framingham score. Blood reduced glutathione (GSH), oxidized glutathione (GSSG), plasma malondialdehyde-(MDA) and 4-hydroxy-2,3-nonenal-(HNE) protein adducts were analyzed.

Results: Significantly greater blood GSSG/GSH ratio and plasma MDA/HNE protein adducts were observed in sarcopenic than in non-sarcopenic patients. A logistic regression model showed a close relationship between serum HNE and MDA adducts and sarcopenia (OR = 1.133, 95% CI 1.057–1.215, and OR = 1.592, 95% CI 1.015–1.991, respectively). Linear and logistic regression analysis evidenced strong associations between the IMT or the Framingham CVD risk category and blood GSSG/GSH or serum HNE protein adducts in the S-O group.

Conclusion: Circulating markers of oxidative stress are increased in sarcopenia and related to CVD risk in sarcopenic obesity, suggesting that redox balance analysis would be a useful part of a multidimensional evaluation in aging. Further research is encouraged to support interventional strategies to correct redox imbalance, which might contribute to the prevention or at least limitation of sarcopenia and its co-morbidities.

1. Introduction

Sarcopenia can be defined as an age-related loss of muscle mass and function associated with poor quality of life and high mortality [1]. Sarcopenia is frequently combined with an increase in body fat, a condition termed sarcopenic obesity [2]. There is no consensus definition of both sarcopenia and obesity in aged subjects; as a consequence, prevalence of sarcopenia and sarcopenic obesity is significantly variable [3]. The co-presence of both sarcopenia and obesity is predictive of worse outcomes than either condition alone [4].

Sarcopenia and obesity share several pathophysiological mechanism which may potentiate each other, synergistically increasing their effect on metabolic disorders, cardiovascular disease and mortality [5]. Thus, the early and correct identification of patients with sarcopenic obesity is extremely important in order to target preventive and therapeutic strategies for those at greatest cardiovascular risk.

Clinical diagnosis of sarcopenia is performed by the assessment of skeletal muscle mass using anthropometry, bioelectrical impedance analysis (BIA) or dual energy X-ray absorptiometry (DEXA). While anthropometric measures and BIA have limited accuracy and validity,

Abbrevations: BIA, bioelectrical impedance analysis; DEXA, dual energy X-ray absorptiometry; BMI, Body Mass Index; HNE, 4-hydroxy-2-nonenal; MDA, malondialdehyde; CVD, cardiovascular disease; LBM, lean body mass; ASM, appendicular skeletal muscle mass; RSMI, relative skeletal muscle mass index; EWGSOP, European Working Group on Sarcopenia in Older People; GSH, oxidized glutathione; GSSG, reduced glutathione; TNF-α, tumor necrosis factor alpha; IMT, intima-media thickness; SDM, standard deviation of the mean; ANOVA, analysis of variance; OR, odds ratio; CI, confidence interval; MNA, Mini Nutritional Assessment

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DEXA provides valid estimates of appendicular skeletal muscle mass, and skeletal muscle measures with DEXA are associated with physical disability [6]. Obesity is defined as Body Mass Index (BMI) ≥ 30 kg/m^2, and central obesity as a waist circumference > 102 cm in men and 88 cm in women, but these criteria are not appropriate in the elderly [7]. Currently, little is known about biological markers of sarcopenia and sarcopenic obesity.

The development of sarcopenic obesity might recognize an intricate interplay of factors including insulin resistance, altered dietary energy, and inflammation [8]. Recent studies suggest pathophysiological links between sarcopenia, sarcopenic obesity and oxidative stress [9]. Oxidative metabolism in skeletal muscle cells produces potentially toxic free radicals which are neutralized by the intracellular antioxidant system. Glutathione plays a central role in detoxification reactions and in the regulation of cellular thiol-disulfide status [10]. One of the indices of systemic oxidative stress is the depletion of circulating glutathione as an index of decreased antioxidant systems in several tissues [11]. A further consequence of oxidative stress is the peroxidation of membrane lipids, a process that leads to alterations in the biological properties of the membrane and to amplification of cellular damage. Lipid peroxidation produces a variety of relatively stable decomposition end products, mainly reactive aldehydes such as 4-hydroxy-2-nonenal (HNE) and malondialdehyde (MDA), which in turn may produce aldehyde-protein adducts measurable in serum as indirect oxidative stress markers [12]. Increasing evidence associates biomarkers of oxidative stress to several human conditions such as obesity, inflammation, aging and cardiovascular diseases [13]. Nevertheless, to date no studies have reported variations of these markers in human sarcopenia as well as sarcopenic obesity. Thus, the present study was designed in order to define whether circulating oxidative stress correlates to sarcopenic obesity in terms of glutathione balance and oxidative protein damage, and whether these biomarkers are associated with cardiovascular disease (CVD) risk in this special sub-population.

2. Methods

2.1. Patients

115 out of 347 elderly outpatients attending the geriatric clinic of the “Casa Sollievo della Sofferenza” hospital in San Giovanni Rotondo (Foggia, Italy) were enrolled. Subjects < 65 years old or with previous diagnosis of ischemic heart disease, stroke, liver cirrhosis, chronic kidney disease, and active cancer were excluded. Further exclusion criteria were chronic bedridden conditions, physical handicap, severe neuro-muscular disease, use of drugs affecting body composition or redox balance, and daily alcohol intake > 40 g. The study was performed according to the Declaration of Helsinki. All patients gave written informed consent.

2.2. Anthropometric and body composition measurements

Baseline evaluation included subjects’ demographics, co-morbidities and socio-economic factors. Height, body weight, and waist circumference were measured according to standardized procedures. Body mass index (BMI) was calculated as the ratio between weight in kilograms and the square of height in meters. The whole-body dual-energy X-ray absorptiometry (DEXA) scan Lunar iDXA™ (GE-Healthcare, Wisconsin, USA) was used for the measurement of fat-free lean body mass (LBM) and percentage of fat mass. Appendicular skeletal muscle mass (ASM) was calculated as the sum of LBM from both arms and legs, according to the method of Heymsfield et al. [14]. Relative skeletal muscle mass index (RSMI) was defined as ASM divided by height (in meter) squared.

2.3. Diagnostic criteria for sarcopenia and obesity

According to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria, after the assessment of gait speed and grip strength, each patient underwent a DEXA measurement and sarcopenia was diagnosed in subjects presenting with a RSMI < 7.25 kg/m^2 (men) or < 5.67 kg/m^2 (women) [1]. Obesity was diagnosed in patients presenting with% fat mass > 27 (men) or > 38 (women).

2.4. Laboratory measurements

Standard laboratory measurements included serum glucose, glycated haemoglobin, insulin, total cholesterol, LDL- and HDL-cholesterol, tryglycerides, creatinine, albumin, uric acid, vitamin D, and microalbuminuria.

A specific enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI) was used to measure plasma tumor necrosis factor alpha (TNF-α), as previously reported [15].

Oxidized (GSH) and reduced (GSSG) glutathione were determined in whole blood as previously described [15].

Plasma fluorescent adducts formed between peroxidation-derived aldehydes (HNE and MDA) and proteins were measured by spectrofluorimetry as previously reported [16].

2.5. Carotid ultrasonography

Bilateral carotid arteries in longitudinal projections were investigated by an experienced operator using an ultrasound instrument (Philips Affiniti 70, Amsterdam, the Netherlands) equipped with a high-resolution broadband width linear array transducer. The participants were examined in the supine position. Each participant had intima-media thickness (IMT) measured on the far wall of the common carotid artery by longitudinal view [17].

2.6. Cardiovascular disease risk assessment

The CVD risk was estimated by the Framingham risk score, based on the Framingham Heart Study (National Heart, Lung, and Blood Institute in Bethesda, MD, USA). The risk score was calculated based on categorical values of age, sex, total and HDL cholesterol, systolic blood pressure, smoking, and diabetes [18]. The participants were then stratified into the following three groups: low risk, presenting with less than 10% CVD risk at 10 years; intermediate-risk, presenting with 10–20% CVD risk at 10 years; high risk, presenting with more than 20% CVD risk at 10 years.

2.7. Statistical analysis

Data were expressed as count and percentages for qualitative values, and as mean ± standard deviation of the mean (SDM) for quantitative variables. Gaussian distribution of the samples was evaluated by Kolgomorov–Smirnov test. The significance of differences between 2 groups (sarcopenic vs non-sarcopenic) was assessed by student’s *t*-test (continuous variables) or in contingency tables by Pearson’s Chi-squared test and Fisher’s exact test (categorical variables). The significance of differences between more than 2 groups was assessed by the one-way analysis of variance (ANOVA) after ascertaining normality by the Kolgomorov-Smirnov test; the Tukey-Kramer was applied as post hoc test. The odds ratio (OR) and the 95% confidence interval (CI) were calculated. Here, ORs > 1 imply a higher chance for SVR relative to the reference category. Linear regression models were used to analyse the association between carotid IMT and GSSG/GSH ratio or serum HNE-protein adducts. Logistic regression models were used to analyse the association between redox measurements and sarcopenia or sarcopenic obesity, as well as between the CVD risk categories according to the Framingham risk score (along with each individual score component)