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Sarcopenia, but not excess weight or increased caloric intake, is associated with coronary subclinical atherosclerosis in the very elderly

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ABSTRACT

Background and aims: Excess weight is a widespread condition related to increased risk of coronary heart disease (CHD). Sarcopenia is a catabolic pathway common of the aging process and also associated with CHD. In the elderly, both changes occur concurrently and it remains unclear the relative contribution on CHD risk. We aimed to investigate whether sarcopenia, excess weight, or both are associated with subclinical atherosclerosis and/or endothelial dysfunction in very elderly individuals.

Methods: We performed a cross-sectional study of cohort enrolled individuals, aged 80 years or older (n = 208), who had never manifested cardiovascular diseases. Blood tests, medical and nutritional evaluations, cardiac computed tomography, flow-mediated dilation (FMD) and physical performance tests were obtained at the study admission. Odds ratio (OR) was calculated by multivariate regression models using coronary calcium score (CCS) categories and FMD as dependent variables. Adjustment for potential confounders was done.

Results: Muscle mass, but not fatty mass, was inversely associated with CCS categories [OR:2.54(1.06−6.06); $p = 0.018$]. The lowering of gait speed was negatively related to CCS>100 [OR:2.36 (1.10−5.06); $p = 0.028$] and skeletal muscle index was directly associated with FMD [OR:5.44 (1.22−24.24); $p = 0.026$]. Total caloric intake was positively related to fatty mass [OR:2.71 (1.09−6.72); $p = 0.031$], but was not related to CCS.

Conclusions: This study reveals that sarcopenia - comprised by reduction of muscle mass and its strength - is associated with subclinical atherosclerosis and endothelial dysfunction. Surprisingly, the excess of fatty mass seems not to be related to atherosclerotic burden in very elderly individuals.

1. Introduction

Excess weight is a worldwide risk factor for coronary heart disease (CHD) [1]. Although this condition is strongly associated with cardiovascular morbidity and mortality in middle-aged adults, the risk remains controversial in elderly individuals, given that excess weight seems to play a protective role in this age group [2]. Evidence points to a U-shaped curve where the resumption of CHD mortality risk occurs with a body mass index (BMI) $\geq$35 kg/m^2 [3]. Paradoxically, several large-scale studies have shown that overweight is related to increased mortality, including cardiovascular causes [4–6].

Among the elderly, the increase in fatty mass is concomitant with the decrease of lean mass, a situation in which adiposity may occur without overweight. Nutritional changes and the prevalence of redistribution of fatty mass to the abdominal region are particular of this age group [7]; both factors may contribute to the development of atherosclerosis.

In the same context of aging, sarcopenia has been defined as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, increasing the risk of adverse outcomes such as physical disability, poor quality of life, and death [8]. Sarcopenia begins at approximately 40 years of age and there is an estimated muscle mass loss of about 8% per decade, stretching until the age of 70 years; after that age, a 15% loss ensues per decade [9]. As added factor, the very process of sarcopenia has been

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previously linked to both an unfavorable metabolic profile and development of atherosclerotic disease, evidenced by the presence of aortic calcification, carotid atherosclerosis, and endothelial dysfunction [10–14].

Worldwide, the proportion of individuals 80 years or older has increased more than other age groups; and a substantial number of them are healthy and suitable for a primary prevention strategy. However, the evidence for this age group is scarce to indicate the contribution of body composition in the development of subclinical atherosclerotic disease. Hence, this study aims to investigate whether sarcopenia, obesity, or both are associated with subclinical cardiovascular disease, in a carefully evaluated cohort of very elderly individuals, in primary prevention setting.

2. Materials and methods

2.1. Participants and study design

For this investigation, we selected participants (n = 208) who were enrolled in the Brasília Study on Healthy Aging (BSHA – ClinicalTrials.gov Identifier: NCT02366104). Briefly, BSHA is a prospective cohort, which was designed to identify markers of cardiovascular risk in very elderly individuals (aged 80 years or older), in a primary prevention setting. The subjects were non-institutionalized and voluntarily accepted to participate in BSHA. They were subsequently followed at the outpatient clinic of the Biocardios Institute of Cardiology (Brasília, Brazil) from December 2008 to August 2011, as described elsewhere [15]. Exclusion criteria were (i) manifested atherosclerotic disease (MI, stroke, or peripheral arterial disease) as indicated by a medical evaluation, electrocardiogram or echocardiogram, (ii) functional dependence or institutionalization, (iii) cognitive impairment assessed by mini-mental state examination (<13 points), (iv) use of any anti-inflammatory drugs in the last 30 days, (v) current or previous diagnosis of immune inflammatory disease, (vi) chronic obstructive pulmonary disease, (vii) glomerular filtration rate <25 mL/min/1.73 m^2, (viii) hepatic disease (aspartate or alanine transaminases ≥1.5 upper reference limit), (ix) chronic infectious disease manifested in the last 3 months, (x) left ventricle ejection fraction <50% on echocardiography and (xi) neoplastic disease at admission or until the first year after enrollment. Neoplastic disease was investigated by evaluation of fecal occult blood, mammography and clinical breast exam, prostate-specific antigen plasma assay, digital rectal examination, and Papanicolaou smear analysis according to current guidelines [16].

The study was carried out in accordance with The Declaration of Helsinki and was approved by the local Ethics Committee (213/08). Participants were only enrolled after they (or their relatives) signed a term of informed consent.

2.2. Clinical evaluation

Study participants from BSHA underwent blood collection for biochemical analysis, imagining tests, physical, clinical and nutritional evaluations, all of them performed in a time interval of up to one week.

Regarding clinical evaluations, ex-smoking status was defined as smoking cessation during at least the last 6 months. Diabetes was defined as the use of anti-diabetic medications, fasting glycaemia ≥126 mg/dL, or glycated hemoglobin (HbA1c) ≥6.5%. Hypertension was defined by the use of antihypertensive drugs, presence of systolic blood pressure (SBP) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg. Sedentary individuals were considered those who do not practice physical activity according to the criteria established by World Health Organization [17].

2.3. Biochemical analysis

Twelve-hours overnight fasting blood samples were collected with EDTA at admission and were centrifuged at 5 °C and at 4500 rpm for 15 min to separate plasma from cells. An automatic chemical analyzer (Hitachi 917, Roche Diagnostics) was used to perform the following analyses: C-reactive protein (CRP; high-sensitivity assay, Cardiophase, Dade Behring, Marburg, Germany), total cholesterol (CHOD-PAP, Roche Diagnostics, Mannheim, USA), high-density lipoprotein cholesterol (HDL-C, Roche Diagnostics, Mannheim, USA), triglycerides (GPO-PAP, Roche Diagnostics, Mannheim, USA), urea and creatinine (GLDH, Hitachi, Tokyo, Japan), glucose (Glucose GOD-PAP, Roche Diagnostics, Mannheim, USA), HbA1c (Variant II, Bio-Rad Laboratories, Hercules, CA, USA). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Glomerular filtration rate (GFR) was estimated by the abbreviated MDRD equation (mL/min/1.73 m^2).

2.4. Physical performance

The adopted cutoffs are recommended by European Consensus on Definition and Diagnosis of Sarcopenia [8]. In case of cutoffs duplicity, it was chosen from the most accurate study in which participants had an average age closer to the individuals of this study [18].

2.4.1. Gait speed

Participants coursed a 2.44 m-long track in their usual pace from a standing start with both feet together on the ground. A timer was activated at the touch of the first foot after the start line. It was paused when the participant's first foot touched the ground beyond the finish line. The test was performed three times, and the mean duration was used to estimate gait speed (m/s). None of the participants used walking aids for the test (i.e., walkers, crutches, etc). The cutoff points for sarcopenia were <0.65 m/s, if height ≤173 cm for male and ≤159 cm for female; and <0.76 m/s, if height >173 cm for male and >159 cm for female.

2.4.2. Handgrip strength

Participants were instructed to remain seated and to keep the dominant arm close to the trunk and with the elbow flexed to a right angle (90°). A mechanical hand dynamometer (Crown, São Paulo, Brazil) was used and grip strength (kgf) expressed as the mean of three measurements with 2-min rest periods intervening. Grip size was individually adjusted for comfort. The cutoff for sarcopenia varied with BMI and in male were ≤29, 30 and 32 kgf, if BMI ≤24, 24.1–28 and > 28 kg/m^2, respectively. In female, the cutoffs were ≤17, 17.3, 18 and 21, if BMI ≤23, 23.1–26, 26.1–29 and > 29 kg/m^2, respectively.

2.5. Assessment of total caloric intake and population-adjusted total energy expenditure

A food frequency intake questionnaire (FFQ) that estimates caloric intake was previously validated in a Brazilian Population [19]. Participants reported the intake of food consumed during the previous 3 months. Their food intake was clustered in 62 items, including the use of nutritional supplements. The approximate portion of usual intake of each item was recalled by patients with the aid of a photographic record for dietary surveys and subsequently quantified in weight. The total caloric intake was calculated based on a food composition database of the Brazilian Table of Food Composition (TACO) [20]. Briefly, TACO is based on a systematic collection of samples of processed food, in triplicate, held in 9 cities that are spread throughout five different geopolitical regions in

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