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Visceral adiposity and skeletal muscle mass are independently and synergistically associated with left ventricular structure and function: The Korean Genome and Epidemiology Study

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ABSTRACT

Background: Obesity and low muscle mass may coexist as age-related changes in body composition. We aimed to investigate the effect of visceral adiposity and skeletal muscle mass on left ventricular (LV) structure and function in the general population.
Methods: A total of 1941 participants without known cardiovascular disease were enrolled from the Korean Genome and Epidemiology Study. Visceral fat area (VFA) was assessed by computed tomography. Appendicular skeletal muscle mass (ASM) was estimated by dual-energy X-ray absorptiometry and was used as a percentage of body weight (ASM/Wt). LV structure and function were assessed by tissue Doppler imaging (TDI) echocardiography.
Results: Across VFA tertiles, ASM increased, but ASM/Wt decreased (all $P < 0.001$). In multivariate models adjusted for conventional cardiovascular risk factors, LV mass index and LV diastolic parameters, such as left atrial dimension, TDI Ea velocity, and E/Ea ratio, were significantly impaired as VFA increased. On the other hand, an increase in ASM/Wt was associated with a decrease in LV mass index and improvement of LV diastolic parameters. With regard to LV mass index and TDI Ea velocity, VFA and ASM/Wt showed synergistic effects (all P interaction <0.05). When both VFA and ASM/Wt were simultaneously included in the same model, both remained independent predictors of LV mass index and TDI Ea velocity.
Conclusions: More visceral fat and less muscle mass are independently and synergistically associated with an increase in LV mass index and impairment of LV diastolic parameters. Further research is needed to explore the complex mechanisms underlying these associations.

1. Introduction

Obesity is associated with increased left ventricular (LV) mass and impairment of LV systolic and diastolic function, and imposes an elevated risk of cardiovascular disease (CVD) independent of comorbid diseases [1–3]. Although body mass index (BMI) is commonly considered a surrogate for obesity, it should be noted that BMI can be an imperfect index as a measure of adiposity because it does not discriminate between fat mass and lean body mass, and does not take into account body fat distribution [4]. The use of the terms "obesity paradox" [5] and "metabolically healthy obesity" [6] based on the BMI suggest that the contributions of visceral fat, muscle mass, and body fat distribution beyond BMI are important when considering the obesity epidemic [7].

The term "sarcopenia" refers to age-related skeletal muscle loss below a critical cutoff value, that is associated with functional impairment and physical disability, although the precise definition is still controversial [8,9]. As aging is related to a gradual loss of skeletal muscle mass and an increase in body fat, the presence of both obesity and

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reduced muscle mass and might independently and additively have a negative effect on a variety of cardiometabolic parameters [10,11]. Despite the fact that muscle mass loss is associated with increased morbidity and mortality in obese individuals, there are few studies on the combined effect of low muscle mass and obesity on LV structure and function in the general population.

Increased LV mass and subclinical LV dysfunction assessed by tissue Doppler imaging (TDI) echocardiography are accepted as useful markers for predicting CVD mortality, even in asymptomatic subjects [12].

The aim of this study was to examine the contribution of visceral adiposity and skeletal muscle mass to LV structure and function in a community-based cohort using the well-validated technique of TDI echocardiography.

2. Methods

2.1. Study population

The study cohort was one of the population-based cohorts included in the Korean Genome and Epidemiology Study and is part of an ongoing prospective investigation. A total of 5015 cohort members were followed biennially from 2001 with scheduled on-site follow-up visits. Information on the study design and the selection criteria for the ongoing prospective study is available in previous reports [13,14]. This cross-sectional study included cohort members who participated in the fifth cycle of the 2-year follow-up study from May 26, 2009, to December 7, 2010. Among 3262 enrolled participants, we excluded 1) participants who did not undergo TDI echocardiography, computed tomography (CT), and dual-energy X-ray absorptiometry (DXA); and 2) participants who had pre-existing cardiovascular disease, congenital heart disease, cardiomyopathy, valvular heart disease, arrhythmia, chronic renal disease, or an ejection fraction below 55%. After excluding a total of 1321 participants, 1941 (934 men and 1007 women) remained eligible for this investigation. Each participant signed an informed consent form that was approved by the Human Subjects Review Committee at the Korea University Ansan Hospital.

2.2. Clinical and laboratory data

According to a site visit schedule for each individual, participants completed interviewer-administered questionnaires on demographic information, medical history and health conditions, family disease history, dietary intake, and lifestyle. The information on physical activity was obtained using interviewer-administered questionnaires. Participants were asked to report hours in a typical day in sleep and five categories of activity intensity (sedentary, very light, light, moderate, and vigorous). A total metabolic equivalent (MET/h) score was calculated by multiplying hours spent by MET values (1.0 for sleep or sedentary, 1.5 for very light, 2.4 for light, 5.0 for moderate, and 7.5 for vigorous activity) [15]. All subjects also completed a comprehensive health examination that included evaluation of anthropometric parameters and collection of biologic specimens for assessment. BMI (kg/m^2) was calculated from height (m) and body weight (kg). Blood samples were delivered to the Seoul Clinical Laboratories (Seoul, Korea) for assays of plasma glucose and insulin, high-sensitivity C-reactive protein (hsCRP), serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride concentrations. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as fasting serum insulin (μU/ml) × fasting plasma glucose (mg/dl) / 405.

2.3. Determination of body composition and visceral fat area

Appendicular skeletal muscle mass (ASM) was estimated using whole body DXA (DPX-MD+, General Electric, Madison, WI, USA). ASM (kg) was defined as the sum of the lean soft tissue masses for the arms and legs. We used ASM as a percentage of body weight (ASM/Wt), as modified from the study of Janssen [16]. The area of abdominal adipose tissue was assessed using a single-slice CT (Brilliance 64; Philips, Cleveland, OH, USA). The scans were conducted at 120 kV exposure without intravenous contrast, with a slice thickness of 5 mm and at the level between the 4th and 5th lumbar vertebra. The total abdominal fat area was delineated by manual tracing within the muscle mass, and the visceral fat area (VFA) was defined as the area with an attenuation range between −190 and −30 Hounsfield units. The subcutaneous fat area was then calculated by subtracting VFA from total abdominal fat area.

2.4. Echocardiography and tissue Doppler imaging

All images were obtained with a commercially available ultrasound (Vivid 7, GE Vingmed, Horton, Norway) using a 4-MHz transducer. Standard M-mode, two-dimensional, and TDI studies were performed according to the guidelines of the American Society of Echocardiography [17]. The LV ejection fraction was calculated from the modified biplane Simpson's method using the apical four- and two-chamber views. The LV mass was determined the Devereux formula and normalized for height to the power of 2.7 as an LV mass index. The left atrial (LA) diameter was measured from the parasternal long-axis view using M-mode measurement. Transmitral pulsed-wave Doppler velocities were recorded from an apical four-chamber view with a 2-mm Doppler sample placed between the tips of the mitral leaflets. The early (E) and late (A) wave velocities, the deceleration time of early filling, and the mitral E/A ratio were all measured from the mitral inflow profile. The pulsed-wave TDI velocities, including the systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities, were measured at the septal mitral annulus using the apical four-chamber view. The mitral E/Ea ratio was subsequently calculated as an index of LV diastolic filling pressure.

2.5. Statistical analyses

Participants were divided into tertiles according to VFA and ASM/Wt. Data were expressed as means ± SD for continuous variables or as percentages for categorical variables. One-way ANOVA or the χ^2 test were used to assess the linear trend of clinical characteristics according to tertiles of VFA or ASM/Wt. The comparison of echocardiographic parameters across tertiles of VFA or ASM/Wt was determined using one-way ANCOVA of general linear models. The interactions between VFA and ASM/Wt on echocardiographic parameters were also tested by including an interaction term in the models. On the basis of clinical relevance and univariate analyses, age, sex, heart rate, systolic blood pressure, fasting glucose, current smoking, current alcohol drinking, total cholesterol, physical activity, anti-hypertensive therapy, and anti-diabetic therapy were regarded as potential covariates in the models. To determine whether both VFA and ASM/Wt were independent predictors of LV structural and functional parameters, additional multivariate linear regression analyses were performed after VFA and ASM/Wt were mutually adjusted in the linear models in addition to the above covariates. Statistical analyses were performed using SAS statistical software (SAS 9.1.3, SAS Institute, Cary, NC, USA) A P values less than 0.05 was considered statistically significant.

3. Results

A total of 1941 study participants aged 50–77 years were included in the present analyses. Mean age was 58 ± 7 years, VFA was 82 ± 38 cm^2, and ASM was 17 ± 4 kg. The demographic and biochemical characteristics of the participants according to tertiles of VFA and ASM/Wt are shown in Table 1. In our study population, a gradual increase in VFA was associated with a worse CV risk factor profile. Individuals with higher VFA were more likely to be older and have higher BMI, systolic and diastolic blood pressure, heart rate, hsCRP, total cholesterol, triglycerides fasting glucose, and HOMA-IR and lower physical activity and HDL cholesterol (all $P < 0.01$). The value of ASM was also higher in subjects with higher VFA ($P < 0.001$). However, when ASM was indexed by body weight and expressed as a percentage, there was a significant negative association between VFA and ASM/Wt ($P < 0.001$). In contrast, as ASM/Wt increased, individuals with higher ASW/Wt were more likely to be younger and have lower BMI, systolic and diastolic blood pressure, total cholesterol, and HOMA-IR and higher physical activity (all $P < 0.05$). There were no significant differences in heart rate, hsCRP, HDL-cholesterol, triglycerides, and fasting glucose according to ASM/Wt tertiles.

Tables 2 and 3 demonstrate the associations of VFA and ASM/Wt with LV structural and functional parameters in multivariate adjusted analyses according to tertiles. As expected, higher VFA was associated with the greater LA size, LV mass index, and E/Ea ratio, whereas the lowest TDI Ea velocity was observed in individuals with the highest VFA. There were no significant differences in LV ejection fraction and TDI Sa velocity according to VFA tertiles. In contrast to the effect of VFA on LV changes, subjects with higher ASM/Wt showed lower values for LA size, LV mass index, and E/Ea ratio, and higher TDI Ea velocity.

Table 4 shows independent associations of VFA and ASM/Wt with LV structural and functional parameters. In the multivariate analyses including VFA and ASM/Wt in the same model in addition to traditional CV risk factors, both of VFA and ASM/Wt were independently associated with LA size, LV mass index, and TDI Ea velocity. However, these independent associations showed an opposite pattern for VFA compared with ASM/Wt, and VFA displayed a stronger association with LV parameters.

Interestingly, there appeared to be a synergistic effect between VFA and ASM/Wt with regard to LV mass index and TDI Ea velocity (Fig. 1). Additional interaction analyses showed a significant interaction of VFA with ASM/Wt for LV mass index (P interaction = 0.003). In addition,