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Low relative muscle mass and left ventricular diastolic dysfunction in middle-aged adults☆,☆☆

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ABSTRACT

Objectives: The association between low skeletal muscle mass and left ventricular diastolic dysfunction (LVDD), a predictor of future heart failure, is largely unexplored. We investigated the relationship between relative muscle mass and LVDD.

Methods: We conducted a cross-sectional study in 67,106 Koreans who underwent an echocardiography as part of a comprehensive health examination between January 2012 and December 2014. Skeletal muscle mass index (SMI) [SMI (%) = total skeletal muscle mass (kg) / body weight (kg) × 100] was estimated using a bioelectrical impedance analyzer. The presence of LVDD was determined using echocardiographic findings.

Results: In 67,106 participants, 19,232 subjects (28.7%) and 1553 subjects (2.3%) had LVDD and left ventricular (LV) hypertrophy, respectively. SMI was positively associated with E/A ratio and septal E′, whereas E/E′ ratio and LV mass index were negatively associated with SMI. Lower SMI was associated with increased presence of LVDD. In a multivariable-adjusted model controlling for potential confounders including physical activity, insulin resistance, and LV mass, the odds ratios for LVDD in SMI quartiles 1, 2, and 3 compared with quartile 4 were 2.11 (1.97–2.25), 1.79 (1.68–1.90), and 1.45 (1.36–1.55), respectively (P for trend < 0.001).

Conclusions: In a large sample of young and middle-aged Korean adults, low relative muscle mass was independently associated with increased risk of LVDD, indicating an independent role of skeletal muscle mass in the pathogenesis of LVDD.

1. Introduction

Left ventricular diastolic dysfunction (LVDD), which is characterized as a filling impairment of the left ventricle (LV), is regarded as a predictor of the development of heart failure (HF) [1]. The prevalence of LVDD increases with age, which is in accordance with the increasing trend of HF incidence with advancing age [1,2]. Coronary artery disease (CAD), hypertension (HTN), type 2 diabetes mellitus (T2DM), and obesity are established risk factors of development of LVDD [3]; however, the pathogenesis and risk factors of LVDD are still not fully understood. Given the tremendous burden of HF, identifying modifiable risk factors of LVDD is crucial for developing strategies that may prevent the onset or improve the prognosis of the disease.

Low skeletal muscle mass or sarcopenia has received significant attention because of the increasing prevalence of elderly individuals worldwide [4]. In addition to the traditional concept of sarcopenia as a geriatric syndrome, recent studies have demonstrated a relationship between sarcopenia and cardiometabolic risk, including T2DM, non-alcoholic fatty liver disease, and subclinical CAD, in the general

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BIA, bioelectrical impedance analyzer; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; FFQ, food frequency questionnaire; HF, heart failure; HEPA, health-enhancing physically active; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; IPAQ-SF, International Physical Activity Questionnaire Short Form; IVST, intraventricular septum thicknesses; LDL-C, low-density lipoprotein-cholesterol; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; OR, odds ratio; PA, physical activity; PWT, posterior wall thickness; SMI, skeletal muscle mass index; T2DM, type 2 diabetes mellitus.

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population across a wide age range that includes asymptomatic young and middle-aged adults [5,6]. Furthermore, insulin resistance is a common feature of low muscle mass and cardiometabolic risk and is also related to LVDD as well as incident HF [7,8]. Therefore, we hypothesized that relative low muscle mass is associated with LVDD, a topic for which there has been little research.

The aims of the present study were to investigate whether relative muscle mass is associated with LVDD in a large sample of asymptomatic apparently healthy young and middle-aged individuals attending a health screening exam and whether this association is independent of LV mass (LVM), insulin resistance, and physical activity (PA).

2. Materials and methods

2.1. Study population

The Kangbuk Samsung Health Study is a cohort of Korean men and women who underwent comprehensive annual or biennial examination at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea [9]. Over 80% of the participants were employees of various companies or local government organizations and their spouses. The health screening exams were paid for by employers under the Korean Industrial Safety and Health Law. The remaining participants voluntarily purchased self-paid screening exams at the health screening center. This study consisted of 72,867 men and women who underwent echocardiography as part of a comprehensive health examination between January 2012 and December 2014.

We excluded 5761 participants for the following reasons (Fig. 1): missing data on skeletal muscle mass by bioelectrical impedance analysis ($N = 781$); a history of a malignancy ($N = 1903$); a history of cardiovascular disease ($N = 922$); and evidence of systolic HF (ejection fraction < 50%), hypertrophic or dilated cardiomyopathy, ischemic heart disease, post-operation or valvular replacement, mitral or atrial stenosis, mitral or atrial regurgitation, atrial fibrillation, or congenital heart disease on echocardiogram ($N = 2418$). As some individuals met more than one exclusion criterion, the total number of patients eligible for the study was 67,106. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, and the requirement for informed consent was waived because we used de-identified retrospective data routinely collected during the health screening process.

2.2. Measurements

All examinations were conducted at Kangbuk Samsung Hospital Health Screening Center clinics in Seoul and Suwon. Data on demographic characteristics, smoking status, alcohol consumption, education level, medical history, and medication use were also collected by standardized, self-administered questionnaires as previously described [9].

PA levels were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) [10]. PA levels were classified into three categories: inactive, minimally active, and health-enhancing physically active (HEPA).

Usual dietary consumption was assessed using a 106-item self-administered food frequency questionnaire (FFQ) designed and validated for use in Korea. The validity and reproducibility of the FFQ were evaluated previously by comparing nutrient and food intake derived from 24-hour dietary recalls over four seasons and a second FFQ administered one year later [11].

Height, weight, and body composition were measured by trained nurses with the participants wearing a lightweight hospital gown and no shoes. Body mass index (BMI) was calculated as height (m) divided by weight (kg) squared (m/kg^2). We classified BMI according to the criteria proposed for Asian populations. The percentages of body fat and skeletal muscle mass were estimated using a multi-frequency bioimpedance analyzer (BIA) with eight-point tactile electrodes (InBody 720, Biospace Co., Seoul, Korea), which was validated with respect to reproducibility and accuracy for body composition [12]. Skeletal muscle mass index (SMI) was calculated as SMI (%) = skeletal muscle mass (kg) / body weight (kg) × 100, based on the methods by Janssen et al. [13]. Class I sarcopenia was classified as muscle mass between -1 and -2 standard deviations (SD) from the mean and class II was classified as muscle mass below -2 SD from the mean of a young reference population (20–39 years old) [6]. Blood pressure (BP) was measured using an automated oscillometric device (Model 53,000; Welch Allyn, New York, USA) while subjects were in a sitting position with the arm supported at heart level. HTN was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or current use of antihypertensive medication.

The methods for measuring serum biochemical parameters including glucose, uric acid, hemoglobin A1c, insulin, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and high-sensitivity C-reactive protein (hsCRP) are described in detail elsewhere [9]. Insulin resistance was assessed using the homeostatic model assessment – insulin resistance (HOMA-IR) equation: fasting blood insulin (uU/mL) × fasting blood glucose (mmol/L)/22.5. T2DM was defined as a fasting serum glucose ≥ 126 mg/dL, hemoglobin A1c ≥ 6.5%, or current use of insulin or anti-diabetic medications.

2.3. Echocardiography

Conventional echocardiography was performed with ultrasound scanners (Vivid 7 and E9, General Electric, Milwaukee, WI, USA) by trained sonographers and measurements were done using a standardized guideline [14]. Linear measurements of left posterior wall thickness (PWT), intraventricular septum thicknesses (IVST), and diameter of the left ventricular cavity at the end of diastole and systole were obtained in M-mode in the parasternal long axis view. LVM was calculated with measurements obtained in M-mode using the following equation: $LVM = 0.8 \times [1.04 \times (LVEDD + IVST + PWT)^3 - LVESD^3] + 0.6$ g [15]. Left ventricular mass index (LVMI) was calculated as $LVM/height^{2.7}$, and LV hypertrophy (LVH) was defined as LVMI ≥ 45 $g/m^{2.7}$ for women and LVMI ≥ 49 $g/m^{2.7}$ for men [14]. The anteroposterior diameter of the left atrium (LA) was measured in all subjects. LA volume was estimated by the biplane area-length method in case of linear measurement of LA diameter was over 40 mm.

To assess diastolic function, pulse-wave Doppler transmitral LV inflow in the apical 4-chamber view was sampled. Early diastolic mitral inflow peak velocity (E), late diastolic peak velocity (A) during atrial contraction, and deceleration time of the E velocity were measured. The early (E′) and late (A′) tissue velocities were measured from tissue Doppler imaging of the septal mitral annulus. Assessment of LVDD was primarily derived from decreased E′ (<8 cm/s) and the cutoff value was according to the European Association of Echocardiography/American Society of Echocardiography [16]. We did not grade diastolic dysfunction because there were several cases in which E/A and E/E′ were discordant and the information for pulmonary vein flow velocities and E/A change during the Valsalva maneuver were not fully measured in all participants.

2.4. Statistical analyses

Characteristics of the study participants were examined according to relative muscle mass index. Categories of SMI comprised the following sex-specific quartiles: for men 27.1–41.2%, 41.3–43.2%, 43.3–45.2%, and 45.3–86.9; for women, 21.7–35.6%, 35.7–37.9%, 38.0–40.1%, and 40.2–49.9%. Age-adjusted mean values (95% CI) of echocardiographic findings were also examined by SMI quartile. To test for linear trends, quartile values were used as continuous variables in regression models.

To determine the association between LVDD and LVH across SMI quartiles, we used a logistic regression model to estimate odds ratios (ORs) with 95% confidence interval (CI). We used four models with progressively increasing adjustment for confounding variables. The basic model was adjusted for age. Additional adjustments were then made for study center (Seoul or Suwon), year of screening exam, smoking history (never, past, current, or unknown), alcohol intake (0, <20, ≥ 20 g/d, or unknown), PA (inactive, minimally active, HEPA, or unknown), level of education (high school graduate or less, community college or university graduate, graduate school or higher, and unknown), and total calorie intake (in quintiles or missing). The analysis was further adjusted for family history of heart disease, history of T2DM, and history of HTN. Finally, the model was further adjusted

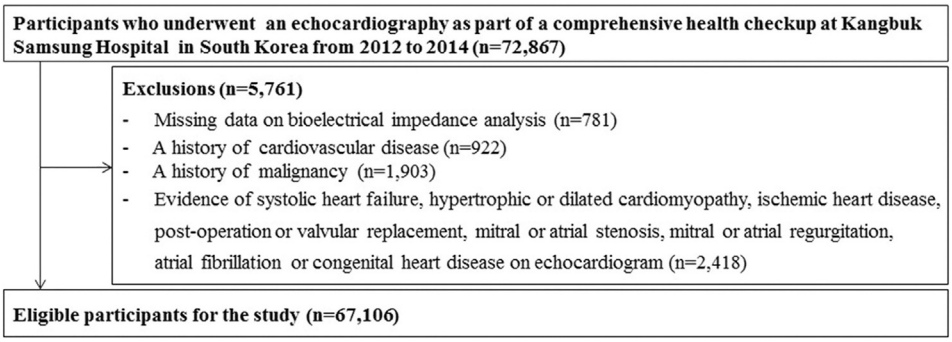

Fig. 1. Flow chart of study participants. As some individuals met more than one exclusion criterion, the total number of subjects included in the study was 67,106.