Research Article

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Sarcopaenia is associated with NAFLD independently of obesity and insulin resistance: Nationwide surveys (KNHANES 2008–2011)

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Background & Aims: Although sarcopaenia is associated with obesity-related comorbidities, its influence on non-alcoholic fatty liver disease (NAFLD) or steatohepatitis has not been fully determined. We aimed to investigate the direct relationship between sarcopaenia and NAFLD or steatohepatitis in the general population.

Methods: We conducted a cross-sectional study using nationally representative samples of 15,132 subjects from the Korea National Health and Nutrition Examination Surveys 2008–2011. Subjects were defined as having NAFLD when they had higher scores from previously validated NAFLD prediction models such as the hepatic steatosis index, comprehensive NAFLD score and NAFLD liver fat score. BARD and FIB-4 scores were used to define advanced fibrosis in subjects with NAFLD. The skeletal muscle index (SMI) [SMI(%) = total appendicular skeletal muscle mass (kg)/weight (kg) × 100] measured by dual-energy X-ray absorptiometry was used to diagnose sarcopaenia with cut points of 32.2% for men and 25.5% for women.

Results: SMI was inversely correlated with all NAFLD predicting scores (Ps <0.001). After stratification, sarcopaenic subjects had an increased risk of NAFLD regardless of obesity (odds ratios [ORs] = 1.55 to 3.02, depending on models; all Ps <0.001) or metabolic syndrome (ORs = 1.63 to 4.00, all Ps <0.001). Multiple logistic regression analysis also demonstrated this independent association between sarcopaenia and NAFLD after adjusting for confounding factors related to obesity or insulin resistance (ORs = 1.18 to 1.22, all Ps <0.001). Furthermore, among the NAFLD population, subjects with lower SMIs were likely to have advanced fibrosis compared with non-sarcopaenic individuals (BARD and FIB-4: ORs = 1.83 and 1.69, respectively; both Ps <0.001). Compared with non-exercised subjects, individuals who exercised regularly had a lower risk of NAFLD (p <0.001), particularly among obese people with well-preserved muscle mass.

Conclusions: Sarcopaenia is associated with increased risks of NAFLD and advanced fibrosis, independent of obesity or metabolic control.

Keywords: Sarcopaenia; NAFLD; Steatohepatitis; Obesity.

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Abbreviations: NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; KNHANES, Korea National Health and Nutrition Examination Survey; ASM, Appendicular skeletal muscle mass; SMI, Skeletal muscle mass index; SD, Standard deviation; BMI, Body mass index; HSI, Hepatic steatosis index; CNS, Comprehensive NAFLD score; LFS, NAFLD liver fat score; HOMA-IR, Homeostasis model assessment of insulin resistance; AST, Aspartate transaminase; ALT, Alanine transaminase; AOR, Adjusted odds ratio.

Introduction

Ageing is becoming a critical public health issue worldwide, particularly in developed societies, as the elderly population has been remarkably increasing. An annual report published by the World Health Organization announced that an average of 22% of the population in high-income countries in 2011 were aged older than 60 years: 31% in Japan, the nation with the highest percentage, 20% overall in Europe and 19% in the United States [1]. Ageing gradually causes the decline in physical function and activity, which are linked to frailty, resulting in a substantial burden on the public health care system as well as impairment in the quality of life for individuals [2]. As one of the key components of frailty, sarcopaenia is regarded as a geriatric syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength [3,4]. Recently, the concept of sarcopaenia is changing: it is now recognised not as an inevitable outcome of ageing, but as a disease condition which could be overcome [5]. Sarcopaenia is more prevalent among elderly people with obesity and exists with various comorbidities [5]. Several cardiometabolic disorders, including diabetes mellitus, metabolic syndrome, and cardiovascular disease, have been associated with sarcopaenia [3,6–8].

Non-alcoholic fatty liver disease (NAFLD) is one of the most common metabolic liver disorders with an estimated

prevalence of ~30% in developed countries [9–11], and its incidence is expected to rise rapidly in the future as the rate of obesity increases, populations become aged, and sedentary lifestyles prevail. NAFLD and sarcopaenia share a similar aetiology such as insulin resistance, which may be ameliorated by the beneficial effect of exercise [12]. Among the categories of NAFLD, non-alcoholic steatohepatitis (NASH) shows a deteriorating nature of chronic liver disease and is associated with increased liver-related mortality by elevating the risk of liver fibrosis, cirrhosis and hepatocellular carcinoma [13–15]. Advanced liver cirrhosis may induce skeletal muscle loss by reducing protein synthesis with increased protein breakdown in muscle [12].

A recent study reported a strong relationship between sarcopaenia and NAFLD, suggesting sarcopaenia as a new risk factor of NAFLD [16]. However, a substantial effect of obesity on NAFLD was not considered and adequately adjusted in this study, which assessed the relationship of NAFLD with sarcopaenic obesity rather than with sarcopaenia itself [17]. Considering the concept that insulin resistance and obesity are the common denominators between sarcopaenia and NAFLD, more robust investigation is necessary to determine the complex association of sarcopaenia with NAFLD. Therefore, we analysed data from the Korea National Health and Nutrition Examination Survey (KNHANES), which is a nationwide cross-sectional study with a nationally representative sample of Korean population annually conducted by the Korea Centre for Disease Control and Prevention to regularly assess the health and nutritional status of general civilians. The aim of this study was to investigate whether the association between sarcopaenia and NAFLD is independent of obesity or metabolic syndrome in the general population. We further evaluated the association between sarcopaenia and NASH in subjects with NAFLD.

Methods

Study participants

The KNHANES is a nationwide, population-based and cross-sectional health examination and survey regularly conducted by the Division of Chronic Disease Surveillance of the Korea Centres for Disease Control and Prevention in the Ministry of Health and Welfare to monitor the general health and nutrition status of South Koreans, as previously described in detail [18]. Similar to the National Health and Nutrition Examination Survey in the United States, each KNHANES is composed of independent datasets of participants from the general population of South Korea. All of the participants were randomly assigned from 600 randomly selected districts of cities and provinces in South Korea.

As depicted in Supplementary Fig. 1, of 37,753 participants from the KNHANES 2008–2011, we initially selected those aged ⩾20 years (12,160 men and 15,911 women). Subjects with missing data for the appendicular skeletal muscle mass (ASM) were excluded (n = 9382). In addition, subjects who met the following criteria were excluded based on our protocol: (1) alcohol consumption >140 g/week for men and 70 g/week for women (n = 2898); (2) positive serologic markers for hepatitis B (n = 561) or hepatitis C virus (n = 28); and (3) the presence of liver cirrhosis (n = 42). This excluded population (n = 3557) was later used for a sensitive analysis. Finally, 15,132 participants (5617 men and 9515 women) were included in the analysis and were divided into four groups according to the presence of sarcopaenia and obesity. Written informed consent was secured from all of the participants before the study began, and the KNHANES was conducted following ethical approval by the Institutional Review Board of the Korea Centre for Disease Control and Prevention (No: 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06C).

Measurements of the appendicular skeletal muscle mass

As previously described [18], ASM was measured using Dual-Energy X-ray Absorptiometry (DXA, QDR 4500A; Hologic Inc., Bedford, MA, USA). The skeletal muscle mass index (SMI) was calculated as follows: SMI (%) = total ASM (kg)/body weight (kg) × 100 [16], which was modified from the study of Janssen *et al.* [19]. This formula was applied based on previous evidence that placing the body weight in the denominator was the best method to minimise the effect of the strong correlation between ASM and body weight [20]. Sarcopaenia was defined as <1 standard deviation (SD) below the sex-specific average for a young reference population from the datasets of KNHANES 2008–2011 (960 men and 1240 women, aged 20–30 years) [6,20]. The cut-off points for sarcopaenia were 32.2% for men and 25.5% for women.

Measurements of clinical parameters and biochemical analysis

KNHANES examined participant demographics and personal and family medical history, including data on anthropometrics, smoking history, physical activity and reproductive health (e.g., early menopause and history of oestrogen replacement therapy) from standardised health questionnaires. Smoking status was categorised as never, ex- and current smoker by self-reporting. Regular exercise was defined as engaging in vigorous exercise on a regular basis (⩾20 min at a time and at least three times per week) [18]. Subjects were considered as obese when the body mass index (BMI) was ⩾25 kg/m^2 based on the criteria of the Asian-Pacific region [21]. Diabetes mellitus was defined based on (1) using insulin or oral hypoglycaemic agents or (2) fasting plasma glucose ⩾126 mg/dl. Impaired fasting glucose was defined as a fasting plasma glucose level of 100–125 mg/dl [22]. Participants were diagnosed as hypertensive if the systolic pressure was ⩾140 mmHg, if the diastolic pressure was ⩾90 mmHg, or if current antihypertensive medication was used.

After overnight fasting for at least 8 h, blood specimens collected from each subject were processed and transported in cold storage to the Central Testing Institute (Neodin Medical Institute, Seoul, Korea). All of the blood samples were analysed within 24 h after transportation. Serum 25-hydroxyvitamin D (25[OH]D) concentration was determined by radioimmunoassay (DiaSorin Inc., Stillwater, MN, USA) using a gamma counter (1470 Wizard; PerkinElmer, Turku, Finland). The serum levels of creatinine and the lipid and liver enzyme profiles were determined using a Hitachi 7600 automated chemistry analyser (Hitachi, Tokyo, Japan) using specific indicated methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The estimated glomerular filtration rate (GFR) was derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [23].

Definition of hepatic steatosis and advanced fibrosis

NAFLD was defined using previous validated fatty liver prediction models [10,24,25] as follows: (1) hepatic steatosis index (HSI) [24]; (2) comprehensive NAFLD score (CNS) [10]; (3) NAFLD liver fat score (LFS) [25]. The BARD [26] and FIB-4 [27] scores were selected as a surrogate index for defining severe conditions of NAFLD (advanced fibrosis). The calculations of BARD and FIB-4 were conducted only in subjects with NAFLD defined using NAFLD prediction models. All prediction models were summarized in Supplementary Table 1.

Statistical analysis

The characteristics of the study subjects were analysed according to the status of obesity and sarcopaenia using Student's *t* test for continuous variables and χ^2 test for categorical variables. Differences in prevalence of NAFLD were assessed using χ^2 test with Bonferroni adjustments. The association between SMI and fatty liver prediction scores (HSI, CNS, and LFS) was evaluated using Chi-square test after transformation of these variables into quartiles. To exclude the effect of obesity or metabolic syndrome, the study population was stratified into two groups depending on the presence of either obesity or metabolic syndrome. Differences in fatty liver prediction scores were also compared using Student's *t* test. Multivariable logistic regression analysis was applied to determine the independent association between sarcopaenia and NAFLD after adjustment for age and sex in model 1 or age, sex, regular exercise, homeostasis model assessment of insulin resistance (HOMA-IR), smoking, and hypertension in model 2. Continuous and categorical variables were expressed as the mean ± SD and n (%), respectively. A *p* value less than