

Relationship between endothelial function and skeletal muscle strength in community dwelling elderly women

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Abstract

Background The aim of this study is to determine whether there is correlation between endothelial function and skeletal muscle function measured by hand grip strength in elderly women.

Methods This cross-sectional study used data of NAMGARAM-2 cohort. The NAMGARAM-2 cohort consisted of a group of people living in three rural communities. They were enrolled for studies on activity limitation due to age-related musculoskeletal disorders including knee osteoarthritis, osteoporosis, and sarcopenia. They were residents aged 40 years or older. They agreed to participate in this cohort from March 2016 to May 2017. Peripheral endothelial function was assessed by reactive hyperaemia-peripheral arterial tonometry using EndoPAT2000 system. Hand grip strength was measured using a digital hand dynamometer.

Results Endothelial function index assessed by EndoPAT was worse in the low grip strength group than that in the normal group of elderly women (1.54 ± 0.51 in the low grip strength group vs. 1.77 ± 0.67 in the normal group, $P = 0.003$). There was a positive correlation between hand grip strength and endothelial function ($r = 0.176$, $P = 0.007$). On stepwise multivariate analysis, endothelial dysfunction (reactive hyperaemia-peripheral arterial tonometry index < 1.67) significantly increased the risk of low hand grip strength (odds ratio = 2.019; 95% confidence interval = 1.107–3.682; $P = 0.022$).

Conclusions Endothelial function and skeletal muscle strength had a significant correlation in elderly women, providing additional support for the relevant role of vascular system in sarcopenia.

Keywords Sarcopenia; Endothelial function; EndoPAT

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Introduction

Sarcopenia refers to decline in muscle mass and strength with age, causing significant impairment in the ability to carry out normal daily functions, and increased risk of falls and fractures, eventually leading to loss of independence.^{1,2} Sarcopenia is not a simple loss of muscle mass and strength

but represents a precursor of frailty and a predictor of increased mortality in chronic diseases.^{3–8} Importantly, sarcopenia increases the risk of physical disability, poor life quality, and mortality.⁹

Recently, some studies suggested that endothelial dysfunction mainly related to insulin resistance might contribute to dysregulation of muscle protein balance in the elderly.¹¹ This

finding highlighted a role of endothelial dysfunction in a progressive loss of skeletal muscle mass and function in patients with diabetes mellitus, whereas diabetes mellitus without sarcopenia also deteriorates endothelial dysfunction.¹¹ In addition, impaired endothelial function measured by plethysmography was more prevalent in patients with heart failure combined with sarcopenia compared with those without.¹²

Because there has been few studies to evaluate the correlation between endothelial function and grip strength that is a well-defining diagnostic tool of sarcopenia, the purpose of this study was to determine whether there was correlation between endothelial function and skeletal muscle function measured by hand grip strength (HGS) in elderly women.

Materials and methods

Ethics statement

All participants provided written informed consent. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital (approval number: GIRB-A16-Y-0012). This study was supported by a grant from the Center for Farmer's Safety and Health funded by the Ministry of Agriculture, Food and Rural Affairs, Republic of Korea.

Participants

This cross-sectional study used data of NAMGARAM-2 cohort. The NAMGARAM-2 cohort consisted of a group of people living in three rural communities. They were enrolled for studies on activity limitation due to age-related musculoskeletal disorders including knee osteoarthritis, osteoporosis, and sarcopenia. They were residents aged 60 years or older who agreed to participate in this cohort from March 2016 to May 2017. At present, 512 people enrolled in the NAMGARAM-2 cohort answered questionnaires and underwent physical examinations, blood tests, and radiographic examination. Participants were excluded if they suffered from cardiovascular disease, cognitive disorder, or malignancy. This study was conducted based on data collected from these examinations.

Health examination survey

Face-to-face survey was conducted by nurses who were informed regarding the objective of this study and trained in data collection procedures. It took approximately 30 min to fill out the questionnaire. The survey included information on sociodemographic variables such as age, sex, level of education, total hours of labour, smoking and drinking status, presence or absence of a spouse, underlying diseases, height,

weight, body mass index (BMI), waist circumference, and blood pressure. Height and body weight were measured with an automatic digital stadiometer (GL-150, G-TECH International Co., Uijungbu, Korea) with clothes on but no shoes. BMI was defined as body weight (kg) divided by square of height (m²).

Nutritional assessment survey

Nutritional status was determined by application of the Mini Nutritional Assessment-short form (MNA-SF). All participants were interviewed by educated investigators using the MNA full form, which includes 18 items (range of scores: 0–30). According to the MNA-SF manual, the MNA-SF score is categorized into two groups: well nourished (≥ 12 points) and high-risk malnourished (≤ 11 points).

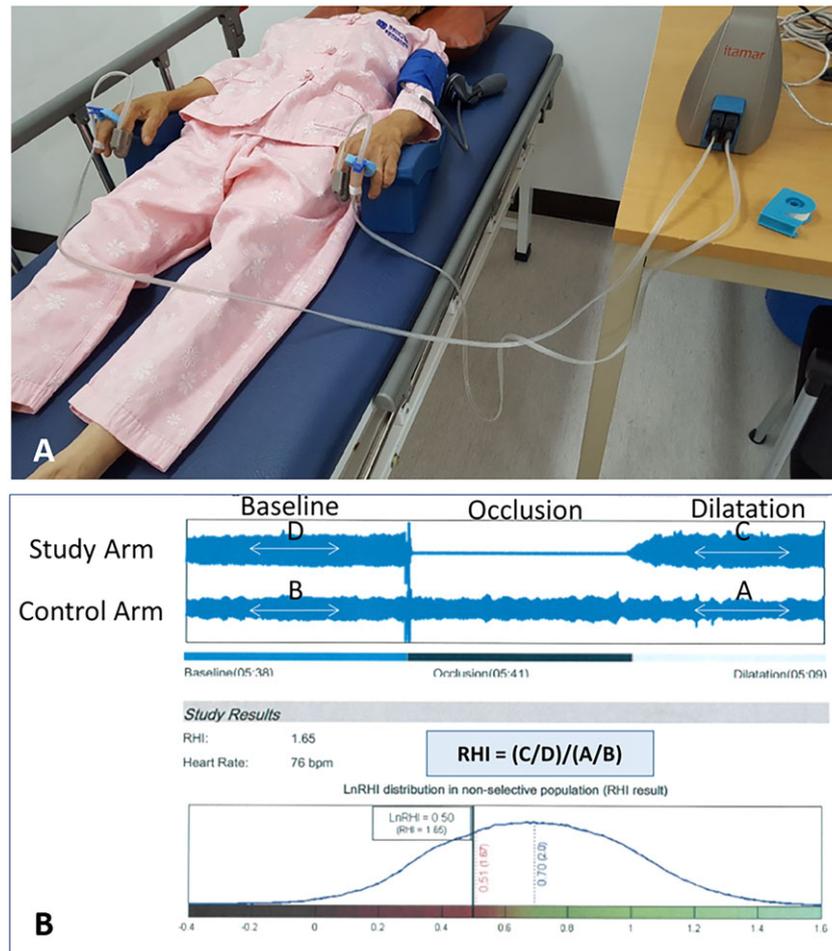
Measurement of endothelial function

Peripheral endothelial function was assessed by reactive hyperaemia-peripheral arterial tonometry (RH-PAT) using an EndoPAT2000 system (Itamar Medical, Caesarea, Israel).^{13–15} RH-PAT measurement is largely operator independent. A computerized algorithm with an online system automatically calculated RH-PAT index. Thus, there was minimal inter-operator and intra-operator variability.^{10–14} RH-PAT studies were performed when patients were in stable and compensated condition after implementing medical therapies for heart failure (HF). They were in fasting state in the early morning before taking any medications. Endothelial function was measured as flow mediated dilation determined with an arterial tonometer in the fingertip (*Figure 1A*). RH-PAT value reflecting the extent of RH was calculated as the ratio of average pulse amplitude of PAT signal over a 1 min time interval starting 1.5 min after cuff deflation (control arm, A; study arm, C) to the average pulse amplitude of PAT signal of 2.5 min time interval before cuff inflation (baseline) (control arm, B; study arm, D). RH-PAT value was calculated with the following equation: RH-PAT value (C/D)/(A/B) (*Figure 1B*). Endothelial dysfunction was defined if RH-PAT index value was low (< 1.67).²⁴

Diagnosis of hand grip strength

Because the measurement of HGS is one of the most commonly used method for the diagnosis of sarcopenia, we defined the presence of sarcopenia based on the values of HGS.¹⁶ HGS was measured using a digital hand dynamometer (Digital grip strength dynamometer, T.K.K 5401, Japan). The measurement of HGS was processed in a standing position with the forearm away from the body at the level of the thigh. Participants were asked to apply maximum grip strength three times with both left and right hands. Between each

Figure 1 (A) Analysis of endothelial function using reactive hyperaemia-peripheral arterial tonometry index (RHI). (B) Calculation of endothelial function using RHI.



RHI; reactive hyperemia-peripheral arterial tonometry index

measurement, at least 30 s of resting interval was allowed. HGS was defined as maximally measured grip strength of the dominant hand.¹⁵ Low HGS was defined according to the criteria set by the Asia Working Group for Sarcopenia (HGS < 26 kg in men and HGS < 18 kg in women).¹⁶

Measurement of body composition and gait speed

Body composition was measured by whole-body dual energy x-ray absorptiometry (GE Medical Systems Lunar, Madison, WI, USA). Bone mineral content, fat mass, and lean soft tissue mass were measured separately for each part of the body, including the arms and legs. The average lean soft tissue masses of the arms and legs were nearly equal to the skeletal muscle mass. As absolute muscle mass correlates with height, the skeletal muscle mass index (SMI) was calculated using the following formula: lean mass = (kg)/height² (m²); lean mass is directly analogous to BMI [BMI = weight (kg)/height² (m²)].

Arm SMI was defined as [arm lean mass (kg)/height² (m²)]. Leg SMI was defined as [leg lean mass (kg)/height² (m²)]. Appendicular SMI was defined as the sum of arm and leg SMI.

Gait speed was measured by asking the participants to walk 6 m at a normal pace, including both the accelerating and decelerating phase.

Sarcopenia was defined according to the Asian Working Group for Sarcopenia criteria for low muscle mass strength (HGS below 18 kg in women and below 26 kg in men) and low muscle strength (appendicular SMI below 5.4 kg/m² in women and below 7.0 kg/m² in men), and low gait speed (below 0.8 m/s).¹⁶

Statistical analysis

To compare means and proportions between groups, Student's *t*-test and Chi-squared (χ^2) test were performed. Pearson correlation analysis was performed to evaluate

the relationship between HGS and endothelial dysfunction. Variables with a *P* value of less than 0.10 in univariate analysis were included in multivariate analysis. Multiple stepwise logistic regression analysis was performed to calculate odds ratio (ORs) and 95% confidence intervals for the association between low endothelial function and the presence of low HGS. All statistical tests were two-tailed. Statistical significance was defined at *P* < 0.05. Statistical analyses were performed using SPSS Statistics V.22 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of elderly women by the presence of low hand grip strength

Of 512 participants, male participants (*n* = 276) were excluded from this study because they did not show any low grip strength based on the reference value. Thus, only 236 elderly women were included in this study. Normal HGS group (*n* = 115) had lower (*P* < 0.001) age, higher (*P* = 0.032) BMI, and higher (*P* < 0.001) gait speed than that of the low HGS group (*n* = 121). The low HGS group showed higher prevalence of osteoporosis than the normal HGS group (*P* < 0.001). The low HGS group also showed higher (*P* = 0.003) prevalence of poor nutritional status than the normal HGS group. In laboratory findings, the low HGS group showed significantly lower levels of haemoglobin (*P* = 0.018), calcium (*P* = 0.013), and protein (*P* = 0.037) but higher (*P* = 0.029) levels of 25-OH vitamin D (Table 1).

The normal endothelial function group (*n* = 89) had lower (*P* = 0.004) prevalence of sarcopenia but higher (*P* = 0.002) HGS than the endothelial dysfunction group (*n* = 147). However, demographic factors or laboratory values were not significantly different between the two groups (Table 2).

On stepwise logistic regression analysis, factors such as endothelial dysfunction, age, BMI, appendicular SMI, radiologic knee osteoarthritis, osteoporosis, gait speed, alcohol, current smoking, hypertension, diabetes mellitus, hypercholesterolaemia, nutritional status, and laboratory findings associated with low grip strength were analysed. Results are shown in Table 3. Endothelial dysfunction (RH-PAT index < 1.67) significantly increased the risk of low HGS (OR = 2.019; 95% confidence interval = 1.107–3.682; *P* = 0.022). Age, osteoporosis (yes/no), and gait speed (≥ 0.8 m/s) were significantly associated with low HGS (OR = 1.171; *P* < 0.001 for age; OR = 2.171; *P* = 0.037 for osteoporosis; and OR = 0.431; *P* = 0.011 for gait speed).

Endothelial function assessed by RH-PAT index was worse in the low HGS group than that in the normal group (1.54 ± 0.51 in the low grip strength group vs. 1.77 ± 0.67 in the normal group, *P* = 0.003). After adjusting for covariates such as age, BMI, gait speed, osteoporosis, diabetes mellitus, poor nutritional status, haemoglobin, serum calcium, 25-OH vitamin D, and total serum protein level, RH-PAT index was significantly different between low HGS group and normal HGS group (1.54 ± 0.58 in the low grip strength group vs. 1.77 ± 0.59 in the normal group, *P* = 0.01) (Figure 2). In addition, there was a positive correlation (*r* = 0.176, *P* = 0.007) between HGS and endothelial function assessed by RH-PAT index (Figure 3).

Table 1 Characteristics of elderly women older than 65 years with the presence or absence of low hand grip strength

Variables	Normal hand grip strength (<i>n</i> = 115)	Low hand grip strength (<i>n</i> = 121)	<i>P</i> -value
Age (years)	71.4 ± 4.4	75.3 ± 4.5	<0.001
BMI (kg/m ²)	24.4 ± 2.9	23.6 ± 3.1	0.032
ASM (kg/m ²)	6.0 ± 0.8	5.8 ± 1.5	0.192
Radiologic knee osteoarthritis (%)	36 (31.3%)	43 (35.5%)	0.491
Osteoporosis (%)	16 (13.9%)	44 (36.4%)	<0.001
Gait speed (<0.8 m/s)	65 (56.5%)	95 (78.5%)	<0.001
Alcohol (%)	5 (4.3%)	11 (9.1%)	0.147
Current smoking (%)	4 (3.5%)	7 (5.8%)	0.401
Hypertension (%)	65 (56.5%)	71 (58.7%)	0.738
Diabetes mellitus (%)	33 (28.7%)	23 (19%)	0.080
Hypercholesterolaemia (%)	17 (14.8%)	14 (11.6%)	0.465
Poor nutritional status (%)	20 (17.4%)	42 (34.7%)	0.003
Laboratory findings			
Haemoglobin (mg/dL)	12.9 ± 1.2	12.6 ± 1.1	0.018
HOMA IR	1.7 ± 1.3	1.5 ± 1.1	0.262
CRP (mg/L)	1.3 ± 2.2	2.6 ± 8.9	0.132
Calcium (mg/dL)	9.4 ± 0.4	9.3 ± 0.3	0.013
25-OH vitamin D (ng/mL)	23.4 ± 9.2	26.2 ± 10	0.029
Total cholesterol (mg/dL)	191.6 ± 41.6	201.2 ± 35.6	0.058
Total protein (g/dL)	7.1 ± 0.4	7.0 ± 0.4	0.037

ASM, appendicular skeletal muscle index; BMI, body mass index; CRP, C-reactive protein; HOMA IR, homeostasis model assessment for insulin resistance.

Table 2 Characteristics of elderly women older than 65 years with the presence or absence of endothelial dysfunction

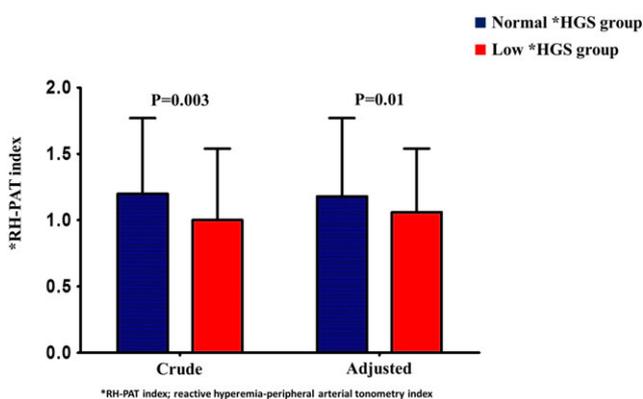
Variables	Normal endothelial function (n = 89)	Endothelial dysfunction (n = 147)	P-value
Age (years)	72.9 ± 4.5	73.7 ± 5	0.212
BMI (kg/m ²)	24.0 ± 3.1	23.9 ± 3.1	0.816
ASM (kg/m ²)	6.0 ± 1.7	5.9 ± 0.7	0.298
Radiologic knee osteoarthritis (%)	30 (33.7%)	49 (33.3%)	0.953
Osteoporosis (%)	18 (20.2%)	42 (28.6%)	0.154
Hand grip strength (kg)	20.3 ± 5.4	18.1 ± 4.8	0.002
Low hand grip strength (%)	35 (39.3%)	86 (58.5%)	0.004
Gait speed (< 0.8 m/s)	57 (64%)	103 (70.1%)	0.337
Alcohol (%)	6 (6.7%)	10 (6.8%)	0.986
Current smoking (%)	7 (7.9%)	4 (2.7%)	0.108
Hypertension (%)	48 (53.9%)	88 (59.9%)	0.371
Diabetes mellitus (%)	25 (28.1%)	31 (21.1%)	0.220
Hypercholesterolaemia (%)	15 (16.9%)	16 (10.9%)	0.188
Poor nutritional status (%)	26 (29.2%)	36 (24.5%)	0.424
Laboratory findings			
Haemoglobin (mg/dL)	12.7 ± 1.2	12.8 ± 1.1	0.704
HOMA IR	1.6 ± 1.2	1.6 ± 1.2	0.771
CRP (mg/L)	1.8 ± 6.2	2 ± 6.9	0.849
Calcium (mg/dL)	9.4 ± 0.4	9.3 ± 0.4	0.858
25-OH vitamin D (ng/mL)	23.7 ± 9.6	25.5 ± 9.8	0.159
Total cholesterol (mg/dL)	197.2 ± 43	196.1 ± 36.2	0.838
Total protein (g/dL)	7.0 ± 0.4	7.0 ± 0.4	0.259

ASM, appendicular skeletal muscle index; BMI, body mass index; CRP, C-reactive protein; HOMA IR, homoeostasis model assessment for insulin resistance.

Table 3 Stepwise logistic regression analysis for low hand grip strength

	B	SE	Exp(B)	95% CI		P-value
				Lower	Upper	
Endothelial dysfunction	0.703	0.306	2.019	1.107	3.682	0.022
Age (year)	0.158	0.036	1.171	1.092	1.257	<0.001
Osteoporosis (yes/no)	0.775	0.371	2.171	1.048	4.495	0.037
Gait speed (≥0.8 m/s)	-0.841	0.331	0.431	0.226	0.825	0.011

CI, confidence interval.

Figure 2 Difference of endothelial function between the normal hand grip strength (HGS) group and low hand grip strength group.

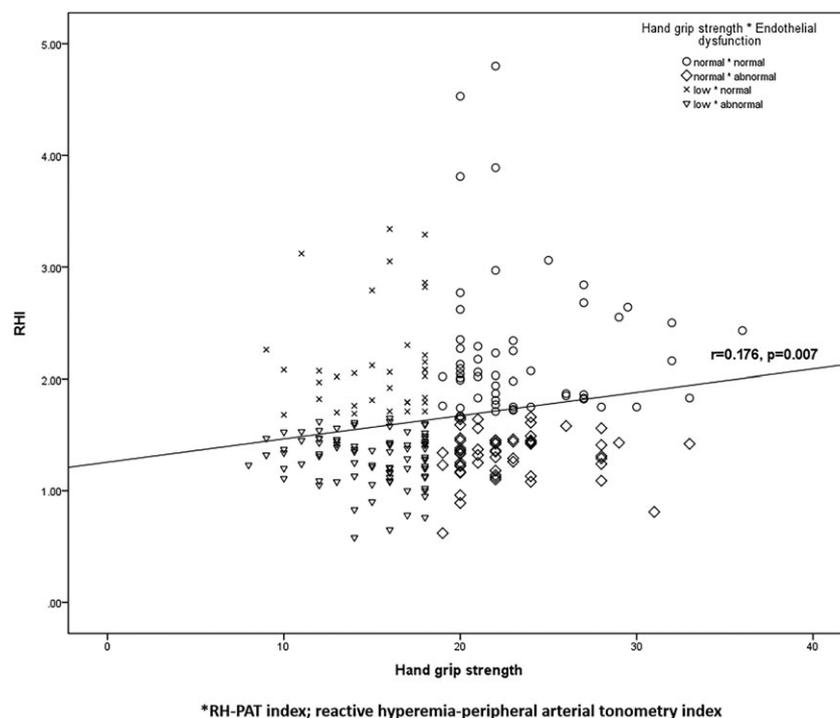
Discussion

This study demonstrated the relationship between endothelial function and skeletal muscle strength. Endothelial function in elderly women assessed by EndoPAT was worse in

the low HGS group than in the normal HGS group. In addition, sarcopenia measured by HGS was positively correlated with endothelial dysfunction. This suggests that endothelial dysfunction might contribute to sarcopenia.

The prevalence of sarcopenia reaches about 30% in Korean elderly population and is expected to increase rapidly due to the effects of ageing.^{17–19} However, Martone *et al.*²⁰ explored the incidence of sarcopenia during hospital stay and the association of different domains with incident sarcopenia in a large sample of hospitalized older patients. They found that sarcopenia develops in approximately 15% of hospitalized elderly patients.

The development of sarcopenia is a heterogeneous process encompassing age-related deficiency of anabolic hormones, activation of pro-inflammatory cytokines, muscle disuse, oxidative stress, and malnutrition.⁹ The present study also demonstrated that age and poor nutritional status could affect the presence of low HGS. In addition, endothelial dysfunction was associated with sarcopenia independent of other risk factors. Indeed, Campos *et al.* demonstrated that sarcopenia was associated with a 3.6-fold increase of subclinical atherosclerotic burden defined by coronary calcium

Figure 3 Correlation between hand grip strength and reactive hyperaemia index.

score.²¹ Moreover, endothelial dysfunction may be a possible pathophysiologic mechanism connecting sarcopenia to cardiovascular disease independent of other well-known cardiovascular risk factors.²²

Besides such clinical correlation between endothelial dysfunction and sarcopenia, many studies have reported molecular biological mechanisms.^{23,24} Weibel *et al.*²⁵ have reported that the hypothesis of symmorphosis predicting structural parameters is matched with functional capacity. In terms of symmorphosis between structure and function, endothelial dysfunction may result in reduced flow through microcirculation. Reduced microcirculation may lead to muscle fibre atrophy.

In molecular biological studies, however, reduced blood flow volume possibly contributes to a negative muscle protein net balance and the development of sarcopenia.²⁶ Indeed, Rasmussen *et al.*²⁷ have reported a strong correlation ($r = 0.90$) between changes in blood flow volume and changes in muscle protein synthesis. The negative muscle protein synthesis by decreased blood volume may be mediated by attenuation of insulin-induced vasodilation in elderly people.²⁶ In the present study, we could not explain the causal relationships between sarcopenia and endothelial dysfunction. Based on various theories, further study is needed to determine such relationship.

Impairment of microcirculation also tends to aggravate metabolic diseases such as diabetes and obesity, whereby

poor skeletal muscle function was frequently observed in patients with these comorbidities. Endothelial dysfunction also leads to decreased secretion of vascular endothelial growth factor (VEGF), thus facilitating functional muscle ischaemia. In an animal study, the expression of VEGF is down-regulated in aged animals. This might lead to impaired VEGF-induced angiogenesis in the ischaemic limb of old mice.²⁸ This impairment of angiogenesis may lead to a reduction in capillary number and subsequent blood flow reduction. Consequently, decreased VEGF related to endothelial dysfunction might lead to negative muscular protein balance and sarcopenia.²⁶

This study has a few limitations. First, this study was designed as cross-sectional study and could not evaluate the causal relationships between reduced grip strength and decreased endothelial function. Second, this study did not evaluate the biological mechanism between the endothelial function and muscle function. Further studies are necessary to demonstrate *in vitro* and *in vivo* molecular mechanisms. Third, we could not rule out the possible effects of medications. However, the prevalence of diseases known to be closely related to endothelial dysfunction was similar between the study groups. Fourth, elderly men were excluded from the present study because that these subjects were farmers living in rural areas. Based on cultural characteristics of Korea, most farmers who work in rural areas are elderly men aged 65 or older and most of them have grip strength above normal levels due to continuous agricultural work.

Therefore, elderly men were excluded from this study because it was difficult to obtain an appropriate hypothesis for the present study using the current sarcopenia reference value. Further study is needed to determine the standard reference value of HGS for Korean farmers. Fifth, dual X-ray absorptometry scan alone was used to measure muscle mass. Additional studies with other muscle mass measurement methods will be needed.²⁹ Finally, any correlation of muscle blood flow with reduced muscle strength may be entirely passive as with reduced muscle mass in a limb there will by definition be reduced blood flow as flow depends on the volume for the muscle vasculature which itself reflects muscle mass.

In conclusion, we demonstrate the correlation between endothelial function and skeletal muscle strength in elderly women. Our finding provides additional support for a relevant role of vascular system in sarcopenia.

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The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017.³⁰

Conflict of interest

None declared by all authors.

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