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SHORT COMMUNICATION

Independent link between peripheral artery disease and muscle wasting in patients with heart failure

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Abstract

Aims A high prevalence of muscle wasting, that is, reduction in muscle mass, in patients with peripheral artery disease (PAD) and heart failure (HF) has been reported. However, whether the association between PAD and muscle wasting is independent of shared risk factors such as diabetes mellitus has not been examined.

Methods and results We retrospectively enrolled 440 HF patients (mean age, 74 years; inter-quartile range, 64–82 years; 52% male). Muscle wasting was defined as an appendicular skeletal muscle mass index (ASMI) of $<$7.0 kg/m^2 in men and $<$5.4 kg/m^2 in women. PAD was defined as an ankle brachial index (ABI) of $<$0.9 in either leg. The prevalence of PAD in HF patients was 21%. ASMI was positively correlated with ABI in HF patients. In multivariate logistic regression analysis, ASMI and muscle wasting were selected as independent explanatory factors of the presence of PAD after adjustment for age, sex, diabetes mellitus, hypertension, dyslipidaemia, estimated glomerular filtration rate, and smoking status, established risk factors of atherosclerosis. In propensity score-matched analysis, frequency of muscle wasting was higher in patients with PAD than in patients with an ABI of $\geqq$1.1 (72.1% vs. 52.5%, P = 0.04).

Conclusions The results suggest that there is an independent link between PAD and muscle wasting in HF patients.

Keywords Atherosclerosis; Diabetes mellitus; Heart failure; Muscle wasting; Peripheral artery disease; Sarcopenia

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Background

Peripheral artery disease (PAD) is a manifestation of systemic atherosclerosis and is associated with an increased risk of functional impairment and cardiovascular mortality.[1] Heart failure (HF) patients frequently have a history of PAD, and PAD was shown to be independently associated with worse clinical outcome in a propensity-matched population of patients with systolic HF.[2] The worse clinical outcome might be simply explained by addition of risk factors of cardiovascular events. However, an alternative explanation might be possible. Although there are apparent overlaps in risk factors for PAD and sarcopenia such as ageing, hypertension, and diabetes mellitus (DM), there is the possibility that PAD is associated with sarcopenia, a risk factor of poor HF prognosis, independently of the shared risk factors.

Aims

In the present study, we examined the association between PAD and muscle wasting in HF patients by using dual-energy X-ray absorptiometry (DEXA) to determine the appendicular skeletal muscle mass index (ASMI).

Methods

This study was conducted in strict adherence with the principles of the Declaration of Helsinki and was approved by the Clinical Investigation Ethics Committee of Sapporo Medical University Hospital.

This study was a single-centre, retrospective, and observational study. We enrolled consecutive patients who were admitted to our institute for diagnosis and management of HF during the period from 1 November 2015 to 30 October 2019. HF was diagnosed according to the Framingham criteria.[3] Data for 440 patients were used for analyses after exclusion of patients with missing data.

Appendicular skeletal muscle mass, the sum of bone-free lean masses in the arms and legs, was analysed by the DEXA scan (Horizon A DXA System, HOLOGIC, Waltham, MA, USA) as previously reported.[4] ASMI was defined as appendicular skeletal muscle mass height.[2] The cut-off values of ASMI for muscle wasting, that is, reduction in muscle mass, were $<$7.00 kg/m^2 in men and $<$5.40 kg/m^2 in women.[5]

Brachial blood pressure (BP) and ankle BP were simultaneously measured using the cuff-oscillometric method (VS-3000TN, Fukuda Denshi Co., Ltd., Tokyo, Japan) in the supine position. The ankle brachial index (ABI) was calculated as the ratio of ankle systolic BP to brachial systolic BP. PAD was defined as an ABI of $<$0.9 in either leg. Based on results of a meta-analysis showing the relationship between ABI and mortality, normal ABI and borderline ABI were defined as following: normal, 1.4 $>$ ABI $\geqq$ 1.1; borderline, 1.1 $>$ ABI $\geqq$ 0.9.[6]

Data are presented as means ± standard deviation or medians (inter-quartile range: 25th–75th percentile) and expressed as frequency and percentage. Intergroup differences for continuous variables and categorical variables were tested using the unpaired Student's *t*-test or Welch's *t*-test. To minimize selection bias of the retrospective study, propensity score matching (1:1 match) was performed according to potential covariates (age, sex, DM, hypertension, dyslipidaemia, ischaemic heart disease, N-terminal pro-brain natriuretic peptide, chronic kidney disease, and smoking status). The statistical significance level was set to $P < 0.05$. All statistical analyses were performed using R Version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics of heart failure patients with peripheral artery disease

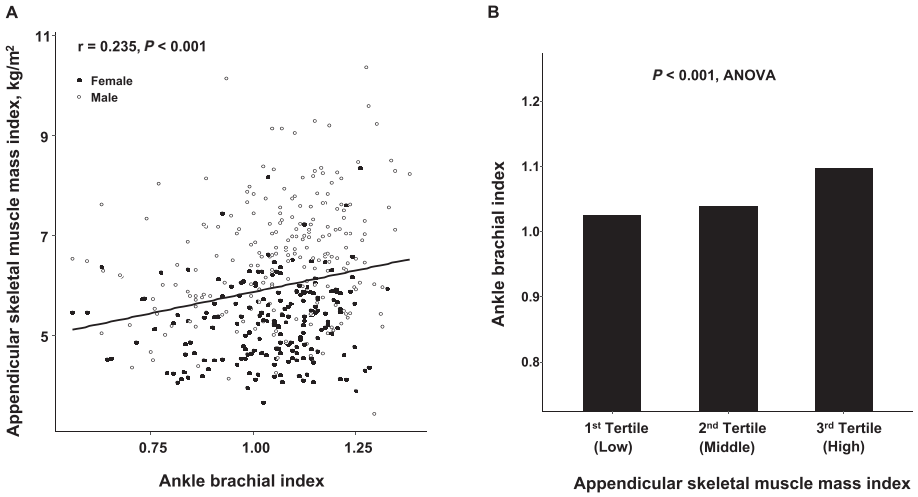
As shown in *Table 1*, the median age of the patients was 74 years (inter-quartile range, 64–82 years), and 52% of the

Table 1 Baseline characteristics

	Overall	Normal (1.1 $\leqq$ ABI $<$ 1.4)	Borderline (0.9 $\leqq$ ABI $<$ 1.1)	PAD (ABI $<$ 0.9)	*P* value
N (%)	440	151	198	91	
Age (years)	74 [64–82]	72 [61–80]	74 [64–82]	78 [70–85]	$<$0.001
Male, *n* (%)	228 (51.8)	95 (62.9)	84 (42.4)	49 (53.8)	0.001
Height (m)	1.58 (0.1)	1.61 (0.1)	1.56 (0.11)	1.57 (0.09)	$<$0.001
Weight (kg)	55.1 [47.1–65.1]	58.7 [49.5–68.7]	54.7 [46.9–63.5]	51.2 [45.8–59.7]	0.001
Body mass index (kg/m^2)	22.4 [19.9–24.6]	22.5 [20.1–25.2]	22.4 [19.8–24.7]	21.7 [19.7–23.8]	0.086
NYHA Class III, *n* (%)	149 (33.9)	47 (31.1)	62 (31.3)	40 (44.0)	0.074
LVEF (%)	50.7 [36.2–64.1]	47.8 [34.7–62.1]	57.1 [40.9–65.0]	47.0 [31.1–62.5]	0.010
LVEF $<$ 40%, *n* (%)	135 (30.7)	53 (35.1)	48 (24.2)	34 (37.4)	0.028
NT-proBNP (pg/mL)	1059 [418–2624]	914 [413–1881]	919 [287–2281]	2141 [919–5852]	$<$0.001
eGFR (mL/min/1.73 m^2)	54.1 [38.5–68.7]	57.8 [40.7–70.8]	55.7 [40.9–69.7]	40.7 [29.4–58.8]	$<$0.001
Co-morbidity, *n* (%)					
Hypertension	274 (62.3)	88 (58.3)	121 (61.1)	65 (71.4)	0.112
Dyslipidaemia	237 (53.9)	77 (51.0)	101 (51.0)	59 (64.8)	0.062
DM	159 (36.1)	45 (29.8)	62 (31.3)	52 (57.1)	$<$0.001
CKD	177 (40.2)	47 (31.1)	77 (38.9)	53 (58.2)	$<$0.001
Medication, *n* (%)					
ACE-I/ARB	199 (45.2)	72 (47.7)	81 (40.9)	46 (50.5)	0.235
Beta-blocker	266 (60.5)	97 (64.2)	107 (54.0)	62 (68.1)	0.038
Loop diuretics	245 (55.7)	74 (49.0)	113 (57.1)	58 (63.7)	0.072
MRA	184 (41.8)	64 (42.4)	75 (37.9)	45 (49.5)	0.177
Aetiology, *n* (%)					$<$0.001
Valvular heart disease	161 (36.6)	35 (23.2)	82 (41.4)	44 (48.4)	
Cardiomyopathy	119 (27.0)	49 (32.5)	52 (26.3)	18 (19.8)	
Ischaemic heart disease	64 (14.5)	20 (13.2)	21 (10.6)	23 (25.3)	
Others	96 (21.8)	47 (31.1)	43 (21.7)	6 (6.6)	

ABI, ankle brachial index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease ($<$60 mL/min/1.73 m^2 of eGFR); DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease.

Figure 1 (A) A scatter plot showing the association between appendicular skeletal muscle mass index and ankle brachial index. (B) Because there are obvious differences in appendicular skeletal muscle mass index between men and women, heart failure patients were subdivided into tertiles within sex as follows: first tertile, <6.04 kg/m^2 in men and <4.87 kg/m^2 in women; second tertile, 6.04 to <7.12 kg/m^2 in men and 4.87 to <5.65 kg/m^2 in women; and third tertile, ≥7.12 kg/m^2 in men and ≥5.65 kg/m^2 in women.



patients were male. The prevalence of PAD in HF patients was 21%. Patients with PAD were older and had higher prevalence of New York Heart Association III symptoms than those without PAD. According to the degree of reduction in ABI, N-terminal pro-brain natriuretic peptide concentration and frequencies of DM, chronic kidney disease, and ischaemic aetiology of HF increased, whereas estimated glomerular filtration rate (eGFR) decreased.

Association of peripheral artery disease with muscle wasting in heart failure patients

In simple linear regression analyses, ASMI was positively correlated with ABI in HF patients (*Figure 1A*). HF patients were subdivided into tertiles within sex and then combined to avoid sex differences. ABI was lower in HF patients with a low tertile of ASMI, whereas it was higher in HF patients with a high tertile of ASMI (*Figure 1B*).

Results of univariate logistic regression analysis showed that ASMI, muscle wasting, age, DM, dyslipidaemia, and eGFR were associated with the presence of PAD (*Table 2*). In multivariate logistic regression analysis, ASMI and muscle wasting were selected as independent explanatory factors of the presence of PAD after adjustment for age, sex, DM, hypertension, dyslipidaemia, eGFR, and smoking status (*Table 2*).

To further exclude the impact of covariates in the association between PAD and muscle wasting, 61 patients with PAD were matched with 61 patients with an ABI of ≧1.1 according to results of the propensity score matching. After the propensity score matching, proportion of patients with DM and HbA1c levels were similar in the two groups (*Table 3*). Comparison of the two groups showed that ASMI tended to be lower and frequency of muscle wasting was significantly

Table 2 Univariate and multivariate logistic regression analysis for peripheral artery disease

	Univariate model			Multivariate Model 1			Multivariate Model 2		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
ASMI (kg/m^2)	0.71	0.57–0.88	0.002	0.62	0.47–0.83	0.001			
Muscle wasting	2.42	1.44–4.06	0.001				2.05	1.19–3.55	0.010
Age (years)	1.03	1.03–1.05	0.002						
Male	1.11	0.70–1.76	0.664						
Hypertension	1.68	1.01–2.77	0.044						
DM	3.02	1.88–4.84	<0.001	2.25	1.35–3.73	0.002	2.25	1.36–3.72	0.002
Dyslipidaemia	1.77	1.10–2.86	0.019						
eGFR (mL/min/1.73 m^2)	0.98	0.97–0.99	0.001						
Never smoker	Reference								
Current smoker	1.62	0.99–2.62	0.051						
Past smoker	0.77	0.31–1.96	0.589						

ASMI, appendicular skeletal muscle mass index; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

Table 3 Comparison of muscle mass after propensity score matching

	Normal (1.1 ≦ ABI < 1.4)	PAD (ABI < 0.9)	*P* value
N	61	61	
Muscle wasting, *n* (%)	32 (52.5)	44 (72.1)	0.040
ASMI (kg/m^2)	5.90 [5.24–6.91]	5.58 [4.74–6.33]	0.081
FMI (kg/m^2)	5.93 [4.65–7.99]	5.71 [4.24–7.23]	0.345
Age (years)	74 [69–81]	77 [68–86]	0.304
Male, *n* (%)	35 (57.4)	36 (59.0)	1
Height (m)	1.61 [1.53–1.67]	1.58 [1.51–1.63]	0.090
Weight (kg)	58.1 [47.1–66.2]	50.6 [43.4–61.5]	0.051
DM, *n* (%)	28 (45.9)	26 (42.6)	0.855
HbA1c (%)	6.1 [5.6–6.4]	6.0 [5.6–6.6]	0.814
FBS (mg/dL)	92 [82–100]	88 [78–105]	0.661
Hypertension, *n* (%)	45 (73.8)	37 (60.7)	0.177
Dyslipidaemia, *n* (%)	38 (62.3)	37 (60.7)	1
Ischaemic heart disease, *n* (%)	10 (16.4)	12 (19.7)	0.814
NT-proBNP (pg/mL)	1390 [723–3768]	1435 [706–4749]	0.776
eGFR (mL/min/1.73 m^2)	46.5 [32.6–63.8]	49.3 [35.4–66.8]	0.609
Smoking status			0.646
Never smoker	26 (42.6)	21 (34.4)	
Past smoker	30 (49.2)	34 (55.7)	
Current smoker	5 (8.2)	6 (9.8)	

ABI, ankle brachial index; ASMI, appendicular skeletal muscle mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FBS, fasting blood glucose; FMI, fat mass index; HbA1c, glycated haemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAD, peripheral artery disease.
Propensity score matching (1:1 match) was performed according to potential covariates including age, sex, DM, hypertension, dyslipidaemia, ischaemic heart disease, NT-proBNP, chronic kidney disease, and smoking status.

higher in patients with PAD than in patients with an ABI of 7≧1.1.

Conclusions

To our knowledge, this is the first study showing an independent link between PAD and muscle wasting. Several potential mechanisms have been proposed. First, patients with PAD have lower exercise capacity due to exercise-induced pain/discomfort in the lower extremities, leading to muscle wasting by reduction in daily physical activity. Thus, muscle wasting in HF patients may be at least partly attributable to presence of PAD. Second, the results of a previous study showed that the calf skeletal muscle area is reduced in patients with PAD, depending on the degree of reduction in ABI.[7] Direct effect of reduction in blood flow on muscle mass may be also involved in the mechanism of the link between PAD and muscle wasting. Third, spurious high ABI due to insufficient compression of tibial artery by high muscle mass might have an impact on results in the present study.[8] Fourth, although covariates that affect the development of PAD and muscle wasting were adjusted in the analyses in the present study, the involvement of shared mechanisms that underlie association between atherosclerotic diseases and muscle wasting, for example, inflammation and oxidative stress, is still possible.[9] On the other hand, the relationship between PAD and muscle wasting may be a mutual. Interestingly, several myokines, muscle-derived cytokines, have been shown to theoretically play a protective role against atherosclerosis.[10,11] Because muscle wasting is frequently observed in HF patients, it is possible that chronic heart failure-induced muscle wasting reduces secretion of myokines, predisposing to the development and exaggeration of PAD. Further analyses are needed to elucidate whether comprehensive management focusing on myokines, for example, pharmacological treatment and rehabilitation for restoration of muscle wasting, may prevent the development and exaggeration of PAD, leading to favourable clinical outcome in HF patients. The limitation of the present study is the use of ABI in the diagnosis of PAD in diabetic patients because results of previous studies suggested that more than 50% of diabetic patients with ABI values between 0.9 and 1.3, that is, normal ABI in the present study, had PAD.[12,13] Furthermore, severity of DM, that is, age at onset, duration, treatment type, and number of complications, was not analysed in the present study, although fasting glucose and HbA1c levels at the time of DEXA measurement were matched (*Table 3*). Thus, the relationship between PAD and muscle wasting in the diabetic patients should be separately analysed in the future study.

Conflict of interest

None declared.

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