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Relationship between serum creatinine to cystatin C ratio and subclinical atherosclerosis in patients with type 2 diabetes

Yoshitaka Hashimoto ,[1,2] Fuyuko Takahashi,[2] Takuro Okamura ,[2] Takafumi Osaka,[2] Hiroshi Okada,[2] Takafumi Senmaru,[2] Saori Majima,[2] Emi Ushigome,[2] Naoko Nakanishi,[2] Mai Asano,[2] Masahide Hamaguchi ,[2] Masahiro Yamazaki,[2] Michiaki Fukui[2]

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[1]Department of Diabetes and Endocrinology, Matsushita Memorial Hospital, Moriguchi, Japan
[2]Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

Correspondence to
Dr Yoshitaka Hashimoto; y-hashi@koto.kpu-m.ac.jp

ABSTRACT

Introduction Sarcopenia index (SI), calculated by (serum creatinine/cystatin C)×100, is reported to be associated with sarcopenia. Few studies reported the association between SI and subclinical atherosclerosis. We evaluated the association between SI and subclinical atherosclerosis, assessed by brachial-ankle pulse wave velocity (baPWV).

Research design and methods One hundred seventy-four patients with type 2 diabetes were included in this cross-sectional study. The relationship between SI and baPWV was assessed by Pearson's correlation coefficient. To calculate area under the receiver operator characteristic (ROC) curve (AUC) of SI for the presence of subclinical atherosclerosis, which was defined as baPWV >1800 cm/s, ROC analysis was performed. Logistic regression analyses were performed to assess the effect of SI on the prevalence of subclinical atherosclerosis adjusting for covariates.

Results Mean age, duration of diabetes, baPWV, and SI were 66.9 (10.1) years, 17.7 (11.6) years, 1802 (372) cm/s, and 77.6 (15.8), respectively. There was an association between SI and baPWV (men; r=−0.25, p=0.001, and women; r=−0.37, p=0.015). The optimal cut-off point of SI for the presence of subclinical atherosclerosis was 77.4 (sensitivity=0.72, specificity=0.58, p<0.001, AUC 0.66 (95% CI: 0.57 to 0.74)). In addition, SI was associated with the prevalence of subclinical atherosclerosis (adjusted OR 0.95, 95% CI: 0.91 to 0.99, p=0.015).

Conclusions SI is associated with the prevalence of subclinical atherosclerosis in patients with type 2 diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sarcopenia is reported to be associated with risk of cardiovascular disease and mortality.
⇒ Serum creatinine/serum cystatin C ratio, called as sarcopenia index, is used as a surrogate marker for sarcopenia.

WHAT THIS STUDY ADDS

⇒ There was an association between sarcopenia index and brachial-ankle pulse wave velocity.
⇒ Sarcopenia index is associated with the prevalence of subclinical atherosclerosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Since sarcopenia index can be evaluated by serum sample, the physicians should pay attention to the patients with low sarcopenia index as the having risk of the presence of subclinical atherosclerosis.

INTRODUCTION

Among patients with diabetes, cardiovascular disease (CVD) is an important cause of morbidity and mortality;[1 2] it is reported that one of the major risk factor for CVD is atherosclerosis, which is a risk for peripheral arterial disease (PAD) and non-embolic ischemic stroke.[3] Type 2 diabetes (T2D) is known to cause atherosclerosis.[4] Subclinical atherosclerosis has been reported to be a risk for cardiovascular events in patients with diabetes.[5 6] Therefore, screening for subclinical atherosclerosis is a useful for identifying high-risk patients including patients with diabetes.[7]

Sarcopenia is becoming an important consideration in older patients with T2D, because the number of older patients with diabetes is increasing.[8] Sarcopenia is reported to be associated with risk of CVD[9] and mortality.[10–12] Serum creatinine (Cre)/serum cystatin C (CysC) ratio, the so-called sarcopenia index (SI), is used as a surrogate marker for sarcopenia.[13–16] Previous studies show that there is an association SI with incident CVD events and mortality.[17 18]

Pulse wave velocity (PWV) is developed as a marker of arterial stiffness[19] and is expressed as the severity of vascular damage;[20] it is a useful tool to detect subclinical atherosclerosis.[21] In particular, brachial-ankle PWV (baPWV) is useful to detect subclinical

atherosclerosis.[22 23] However, few studies revealed the association between SI and subclinical atherosclerosis. Therefore, in this cross-sectional study, we used baPWW to evaluate the relationship between SI and subclinical atherosclerosis.

MATERIALS AND METHODS

Study participants

In this cross-sectional study, we extracted the data from the KAMOGAWA-DM cohort study, which is an ongoing prospective cohort study.[24] To clarify the natural history of patients with diabetes, we invited all patients with diabetes who were outpatients of Department of Endocrinology and Diabetes of Kyoto Prefectural University of Medicine Hospital (Kyoto, Japan) or Department of Diabetes of Kameoka Municipal Hospital (Kameoka, Japan) to participate in the KAMOGAWA-DM cohort study and enrolled those who agreed to participate. In this study, we extracted the data of patients who were registered from November 2016 to December 2017.[25] Exclusion criteria were as follows: non-T2D, no data of baPWV, no data of CysC, renal dysfunction (defined as serum Cre >2.0 mg/dL),[26] missing data of body weight, history of CVD, including heart failure, unstable angina, myocardial infarction, stroke, and peripheral artery disease (defined as ankle-brachial index <0.9).[27]

Data collection and measurements

Body mass index (BMI) was assessed as weight (kg) divided by height^2 (m^2). Using a standardized self-administered questionnaire, the data of habitual alcohol consumption (consuming alcohol daily or not), smoking status (current smoker or not), and exercise habit (exercise of some kind at least once a week or not) were obtained. Usage of medications for hypertension and diabetes, including insulin, sulfonylurea, glinide, dipeptidyl peptidase-4 inhibitors, biguanide, thiazolidine, alpha-glucosidase inhibitors, sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonist (GLP-1RA), and dyslipidemia, including statin, were obtained from medical records.

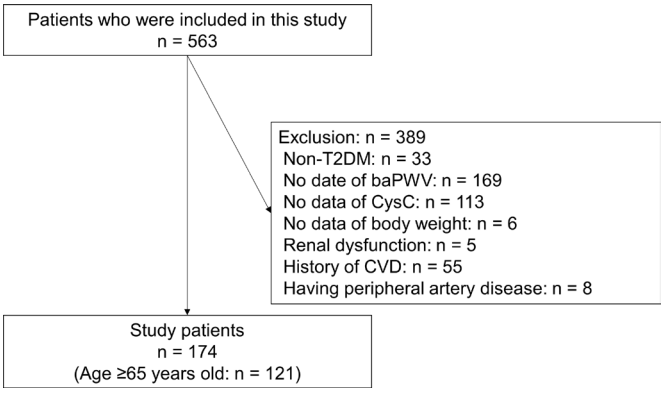

Figure 1 Inclusion and exclusion flow. baPWV, brachial-ankle pulse wave velocity; CVD, cardiovascular disease; CyC, cystatin C; T2DM, type 2 diabetes.

Table 1 Clinical characteristics of study participants

	All n=174
Age, years	66.9 (10.1)
Men, % (n)	56.3% (98)
Duration of diabetes, years	17.7 (11.6)
Family history of diabetes, % (n)	46.0% (80)
Height, cm	161.5 (9.5)
Body weight, kg	61.7 (12.3)
Body mass index, kg/m^2	23.5 (3.5)
Systolic blood pressure, mm Hg	128.3 (15.4)
Diastolic blood pressure, mm Hg	73.3 (10.3)
Medication for hypertension, % (n)	46.6% (81)
Insulin, % (n)	25.4% (41)
Sulfonylurea, % (n)	31.0% (54)
Glinide, % (n)	16.7% (29)
Dipeptidyl peptidase-4 inhibitors, % (n)	62.6% (109)
Biguanide, % (n)	47.7% (83)
Thiazolidine, % (n)	2.3% (4)
Alpha-glucosidase inhibitors, % (n)	16.7% (29)
Sodium glucose co-transporter 2 inhibitors, % (n)	21.3% (37)
Glucagon-like peptide-1 receptor agonist, % (n)	10.9% (19)
Statin, % (n)	42.0% (73)
Current smoker, % (n)	14.4% (25)
Exerciser, % (n)	57.5% (100)
Habitual alcohol consumption, % (n)	32.7% (56)
HbA1c, mmol/mol	56.5 (10.0)
HbA1c, %	7.3 (0.9)
Plasma glucose, mmol/L	8.1 (2.2)
Creatinine, mg/dL	0.76 (0.23)
Cystatin C, mg/dL	0.99 (0.26)
Sarcopenia index	77.6 (15.8)
Brachial-ankle pulse wave velocity, cm/s	1802 (372)
Subclinical atherosclerosis, % (n)	43.7% (76)

HbA1c, hemoglobin A1c.

Serum was collected after an overnight fast. Serum Cre and CysC levels were measured. SI was calculated as (serum Cre divided by serum CysC)×100.

After at least 5 min of rest in the supine position, the baPWV was measured using a Colin Waveform analyser (PWV/ABI, Colin Medical Technology, Komaki, Japan) as well as both arm and ankle blood pressure. The details of this method have been described elsewhere.[28] The Pearson's correlation coefficients of interobserver and intraobserver reproducibility were r=0.98 and r=0.87, respectively.[28] The higher baPWV, with both sides measured, was used as representative for each patient. At same time, the lower ABI, with both sides measured, was

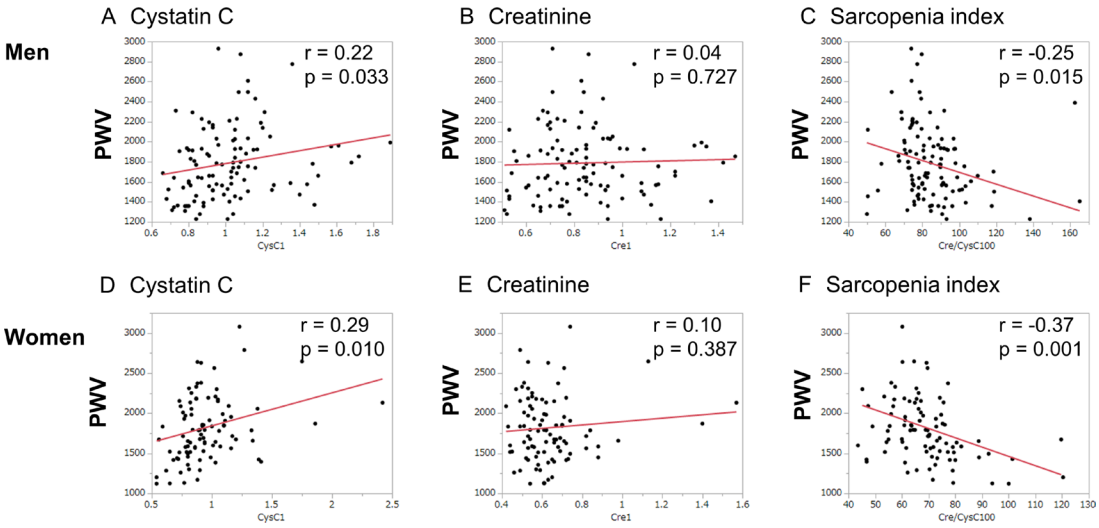

Figure 2 Correlation between cysteine C (CysC), creatinine (Cre), or sarcopenia index and brachial-ankle pulse wave velocity (PWV). (A–C) Correlation between cysteine C, creatinine, or sarcopenia index and brachial-ankle PWV among men. (D–F) Correlation between cysteine C, creatinine, or sarcopenia index and brachial-ankle PWV among women.

used as representative for each patient. A baPWV >1800 cm/s was defined as subclinical atherosclerosis.[22]

Statistical analysis

The statistical analyses were carried out using the JMP V.13.2.1 software (SAS Institute, Cary, North Carolina, USA). Statistical significance was set at p value <0.05.

Continuous variables were expressed as mean (SD) and categorical variables were expressed as percentage (%) (number). The relationships between CysC, Cre, or SI and baPWV were evaluated by Pearson's correlation coefficient. The receiver operating characteristic (ROC) analysis was used to calculate area under the ROC curve (AUC) of CysC, Cre, or SI for the presence of subclinical atherosclerosis. Then, logistic regression analyses were performed to evaluate the effect of CysC, Cre, or SI on the presence of subclinical atherosclerosis, adjusting for age, sex, BMI, smoking status, exercise habit, systolic blood pressure, hemoglobin A1c (HbA1c), antihypertensive medication, insulin, SGLT2i, GLP-1RA, and statin usage. Furthermore, subanalyses were performed for patients aged ≥65 years.

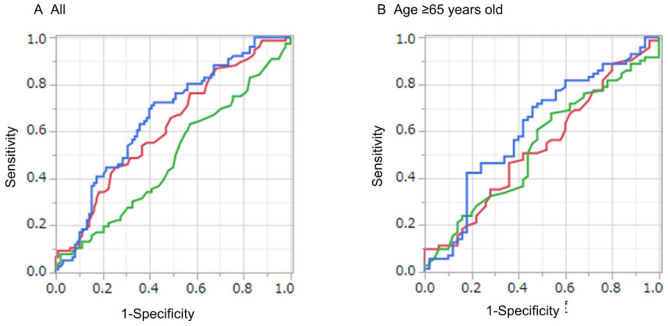

Figure 3 Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) of cysteine C, creatinine, or sarcopenia index for subclinical atherosclerosis. (A) All patients. Red line represents cysteine C (AUC 0.62, 95% CI 0.53 to 0.70), green line represents creatinine (AUC 0.49, 95% CI 0.40 to 0.57), and blue line represents sarcopenia index (AUC 0.66, 95% CI 0.57 to 0.74). The p values of difference of AUC of cysteine C and creatinine, cysteine C and sarcopenia index, and creatinine and sarcopenia index were <0.001, 0.449, and 0.023, respectively. (B) Patients aged ≥65 years. Red line represents cysteine C (AUC 0.53, 95% CI 0.43 to 0.64, p=0.071), green line represents creatinine (AUC 0.53, 95% CI 0.43 to 0.64), and blue line represents sarcopenia index (AUC 0.61, 95% CI 0.51 to 0.71). The p values of difference of AUC of cysteine C and creatinine, cysteine C and sarcopenia index, and creatinine and sarcopenia index were 0.992, 0.272, and 0.071, respectively.

RESULTS

Five hundred sixty-three patients were included in this cross-sectional study. After excluding 389 patients, 174 patients were selected for this study (figure 1). The clinical characteristics of this study patients are shown in table 1. Mean age, duration of diabetes, and baPWV were 66.9 (10.1) years, 17.7 (11.6) years, and 1802 (372) cm/s, respectively. The proportion of subclinical atherosclerosis was 43.7% (n=76).

Data were expressed as mean (SD) or number (%). SI was calculated as (serum Cre divided by serum cystatin C)×100.

Figure 2 represents the association between CysC, Cre, or SI and baPWV. CysC and SI were related to baPWV, whereas Cre was not related to baPWV in both sexes (figure 2).

The AUC of SI for the prevalence of subclinical atherosclerosis (0.66 (95% CI: 0.57 to 0.74)) was superior for that of Cre (0.49 (95% CI: 0.40 to 0.57), p=0.023). Furthermore, the optimal cut-off point of SI for the prevalence of subclinical atherosclerosis was 77.4 (sensitivity=0.72, specificity=0.58, p<0.001) (figure 3A).

Table 2 shows the ORs of CysC, Cre, and SI for the presence of subclinical atherosclerosis. After adjusting for

Table 2 Logistic regression analyses for the presence of subclinical atherosclerosis

All patients (n=174)	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, year	1.21 (1.12 to 1.30)	<0.001	1.20 (1.11 to 1.29)	<0.001	1.19 (1.11 to 1.28)	<0.001
Men	0.94 (0.35 to 2.52)	0.897	0.70 (0.29 to 1.68)	0.422	1.60 (0.53 to 4.85)	0.406
Exercise habit	1.15 (0.49 to 2.70)	0.75	1.04 (0.44 to 2.43)	0.937	1.03 (0.44 to 2.44)	0.938
Current smoker	0.82 (0.26 to 2.59)	0.735	0.87 (0.26 to 2.88)	0.82	0.70 (0.20 to 2.42)	0.569
Systolic blood pressure, mm Hg	1.06 (1.03 to 1.09)	<0.001	1.06 (1.03 to 1.09)	<0.001	1.06 (1.03 to 1.09)	<0.001
Body mass index, kg/m^2	0.88 (0.76 to 1.02)	0.098	0.85 (0.73 to 0.99)	0.039	0.85 (0.74 to 0.99)	0.031
HbA1c, %	1.61 (0.94 to 2.76)	0.084	1.55 (0.90 to 2.66)	0.112	1.68 (0.95 to 2.95)	0.074
Medication usage for hypertension	1.60 (0.66 to 3.88)	0.299	1.43 (0.60 to 3.43)	0.424	1.38 (0.56 to 3.36)	0.484
Insulin usage	0.93 (0.35 to 2.51)	0.889	0.89 (0.33 to 2.40)	0.821	0.83 (0.30 to 2.30)	0.721
SGLT2i usage	2.51 (0.72 to 8.71)	0.148	2.99 (0.87 to 10.4)	0.083	2.72 (0.78 to 9.50)	0.117
GLP-1RA usage	2.80 (0.61 to 12.8)	0.184	2.31 (0.52 to 10.4)	0.274	2.48 (0.55 to 11.2)	0.239
Stain usage	0.34 (0.14 to 0.85)	0.021	0.35 (0.14 to 0.87)	0.023	0.33 (0.13 to 0.86)	0.023
Creatinine, mg/dL	0.26 (0.02 to 2.80)	0.263	—	—	—	—
Cystatin C, mg/dL	—	—	1.51 (0.24 to 9.60)	0.658	—	—
Sarcopenia index, Δ1 incremental	—	—	—	—	0.95 (0.91 to 0.99)	0.015
Patients aged ≥65 years (n=121)	**Model 1**		**Model 2**		**Model 3**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, year	1.08 (0.97 to 1.20)	0.139	1.07 (0.96 to 1.18)	0.22	1.06 (0.96 to 1.18)	0.242
Men	0.76 (0.24 to 2.41)	0.644	0.62 (0.22 to 1.78)	0.376	1.75 (0.46 to 6.69)	0.416
Exercise habit	0.91 (0.35 to 2.39)	0.849	0.83 (0.31 to 2.21)	0.712	0.82 (0.31 to 2.19)	0.69
Current smoker	0.71 (0.16 to 3.16)	0.658	0.67 (0.15 to 2.95)	0.596	0.54 (0.11 to 2.58)	0.439
Systolic blood pressure, mm Hg	1.08 (1.04 to 1.12)	<0.001	1.08 (1.04 to 1.12)	<0.001	1.08 (1.04 to 1.13)	<0.001
Body mass index, kg/m^2	0.82 (0.69 to 0.98)	0.026	0.79 (0.66 to 0.94)	0.01	0.79 (0.66 to 0.95)	0.007
HbA1c, %	1.38 (0.66 to 2.90)	0.397	1.25 (0.59 to 2.61)	0.561	1.33 (0.62 to 2.89)	0.464
Medication usage for hypertension	1.59 (0.56 to 4.59)	0.385	1.39 (0.48 to 3.99)	0.543	1.48 (0.51 to 4.29)	0.466
Insulin usage	0.93 (0.31 to 2.83)	0.901	0.91 (0.30 to 2.78)	0.867	0.74 (0.23 to 2.32)	0.599
SGLT2i usage	2.28 (0.51 to 10.1)	0.279	2.76 (0.62 to 12.4)	0.184	2.47 (0.54 to 11.4)	0.245
GLP-1RA usage	4.34 (0.58 to 32.3)	0.152	3.44 (0.50 to 23.9)	0.211	3.95 (0.54 to 28.8)	0.175
Stain usage	0.31 (0.11 to 0.90)	0.031	0.32 (0.11 to 0.94)	0.038	0.25 (0.08 to 0.80)	0.019
Creatinine, mg/dL	0.43 (0.03 to 5.96)	0.531	—	—	—	—
Cystatin C, mg/dL	—	—	2.45 (0.27 to 21.9)	0.424	—	—
Sarcopenia index, Δ1 incremental	—	—	—	—	0.94 (0.89 to 0.99)	0.017

Sarcopenia index was calculated as (serum creatinine divided by serum cystatin C)×100.
GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; SGLT2i, sodium glucose co-transporter 2 inhibitors.

covariates, SI was related to the prevalence of subclinical atherosclerosis (OR 0.95, 95% CI: 0.91 to 0.99, p=0.015), whereas CysC (OR 1.51, 95% CI: 0.24 to 9.60, p=0.658) or Cre (OR 0.26, 95% CI: 0.02 to 2.80, p=0.263) was not.

Subanalyses of patients aged ≥65 years were also performed. SI was associated with baPWV, whereas CysC or Cre was not associated with baPWV in both sexes (figure 4). In addition, the AUC of SI for the prevalence of subclinical atherosclerosis (0.61 (95% CI: 0.51 to 0.71)) tended to be superior to that of Cre (0.53 (95% CI: 0.43 to 0.64), p=0.071). Furthermore, the optimal cut-off point of SI for the prevalence of subclinical atherosclerosis was 77.2 (sensitivity=0.70, specificity=0.54, p=0.044) (figure 3B). SI was related to the prevalence of subclinical atherosclerosis (OR 0.94, 95% CI: 0.89 to 0.99, p=0.017), whereas CysC (OR 2.45, 95% CI: 0.27 to 21.9, p=0.424) or Cre (OR 0.43, 95% CI: 0.03 to 5.96, p=0.531) was not, after adjusting for covariates (table 2).

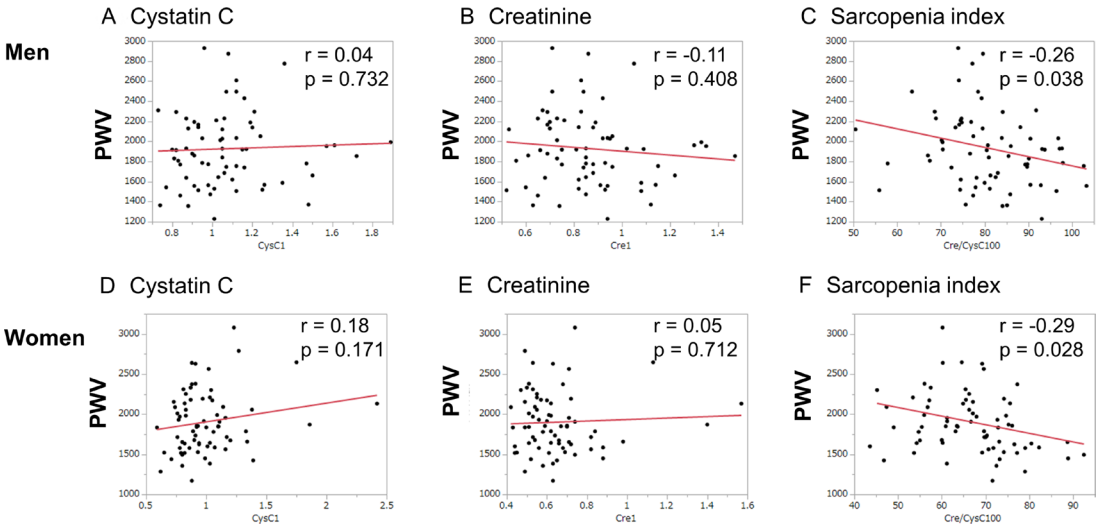

Figure 4 Correlation between cysteine C (CysC), creatinine (Cre), or sarcopenia index and brachial-ankle pulse wave velocity (PWV) among patients aged ≥65 years. (A–C) Correlation between cysteine C, creatinine, or sarcopenia index and brachial-ankle PWV among men. (D–F) Correlation between cysteine C, creatinine, or sarcopenia index and brachial-ankle PWV among women.

DISCUSSION

In this study, we investigated the association between SI and subclinical atherosclerosis in patients with type 2 diabetes mellitus (T2DM) and clarified that there is an association of SI with baPWV and the prevalence of subclinical atherosclerosis.

A recent meta-analysis showed that the proportion of sarcopenia in patients with T2DM was higher than that in people without T2DM.[29] Sarcopenia is reported to be associated with a risk of atherosclerosis,[30–34] CVD[9 35–38] and mortality.[10–12] Recent studies showed that SI is useful marker for sarcopenia and physical activity levels.[13–15 39] In addition, SI is reported to be associated with incident CVD[17 18] and mortality.[17 40–42] However, little is known about the association between SI and subclinical atherosclerosis. Recently, Shin[43] revealed that there was an association between SI and carotid plaque score in patients with T2DM.

A possible explanation for the association between SI and subclinical atherosclerosis is discussed below. In sarcopenia, the balance between muscle catabolism and synthesis is disrupted due to suppression of the proliferative signaling pathway of skeletal muscle cells and overactivation of the apoptotic signaling pathway.[44] Malnutrition, physical inactivity, oxidative stress, hormonal changes, inflammation, insulin resistance, autophagy, and apoptosis and have been implicated in the development of both CVD and sarcopenia.[45] Sarcopenia and CVD are closely related through insulin resistance, inflammation, and oxidative stress.[44] For example, increased interleukin (IL)-6, which is associated with the degree of atherosclerosis in older patients,[46] encourages the catabolism of skeletal muscle and muscle atrophy.[47] Increased reactive oxygen species (ROS) causes vasoconstriction and encourages arterial hypertension, promotes the formation of atherosclerotic plaques, and causes vascular endothelial dysfunction.[44] The accumulation of ROS leads to sarcopenia by promoting muscle hydrolysis; at the same time, it affects muscle protein synthesis via nitrification.[48] In addition, high palmitic acid intake leads to muscle atrophy[49] and CVD[50] through increasing ROS. These mechanisms are involved in SI and subclinical atherosclerosis.

The limitations of our study should be mentioned. First, since our study is a cross-sectional study, casual nexus is unknown and further follow-up study is needed to clarify this relationship. Second, relatively small number of participants, so there is a possibility that it may not accurately represent the study population. The characteristics, including sex, smoking, BMI, and HbA1c, were not different between analysis group and exclusion group (men, 56.3% vs 60.9%, p=0.304; smoker, 14.4% vs 13.3%, p=0.741; BMI, 23.5 (3.5) vs 24.1 (4.3) kg/m^2, p=0.304; and HbA1c, 7.3 (0.9) vs 7.2 (0.9) %, p=0.163), although age of the analysis group was lower than that of exclusion group (66.9 (10.1) vs 70.4 (10.2) years, p<0.001). Third, measurement of markers of inflammation and oxidative stress, such as serum IL-6, 4-hydroxynonenal, and urinary 8-OH-dG may support our hypothesis. Unfortunately, however, we did not measure these markers. Lastly, we only included Japanese patients, thus, it is uncertain that the results of this study generalized to non-Japanese populations, especially non-Asian populations.

In conclusion, SI is associated with the presence of subclinical atherosclerosis in patients with T2DM and this has implications for the management of these patients. Further large-scale prospective studies are needed to clarify the causal nexus.

Contributors YH designed the study, researched, analyzed, and interpreted data and wrote manuscript; FT researched and interpreted data and contributed to discussion; TOk, TOs, TS, HO, SM, EU, NN, and MA researched data and contributed

to discussion; MH conceptualized the study, researched data, and contributed to discussion; MY researched data and contributed to discussion; MF conceptualized the study, researched data, and contributed to discussion. All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript. YH is responsible for the overall content as guarantor.

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ORCID iDs
Yoshitaka Hashimoto http://orcid.org/0000-0002-8794-0550
Takuro Okamura http://orcid.org/0000-0001-7269-1697
Masahide Hamaguchi http://orcid.org/0000-0002-8651-4445

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