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Original

Relationship between Increased ba-PWV Values and Body Composition in Patients with Type 2 Diabetes Mellitus

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Summary

Background: Reduced lower limb circumference in patients with type 2 diabetes mellitus (T2DM) could be a useful screening tool for arteriosclerosis. The objective of this study was to clarify the relationship between lower limb circumference and body composition measures, muscle strength, patient characteristics, and the progression of arteriosclerosis in patients with T2DM.

Methods: We included 114 patients receiving outpatient care for T2DM, assessed body composition, muscle strength indicators, patient characteristics, clinical diabetic neuropathy status, and examined their brachialankle pulse wave velocity (ba-PWV) measurements using multiple regression analysis.

Results: The ba-PWV severity levels were classified at 1400 cm/s, 1650 cm/s, and 1963 cm/s to investigate their associations with the patients' attributes using logistic regression analysis. Body mass index (BMI), HbA 1c levels, abnormal ankle reflex, and the percentage ratio of the circumference at the tibial tuberosity to the maximum circumference of the lower leg (TRSC%: Circumferential diameter of tibial rough surface/Circumferential diameter of tibia, at the calf at the proximal 26% of the fibula) were the independent variables in the multiple regression analysis, with ba-PWV as the dependent variable. In the logistic regression analysis of ba-PWV categorized at 1400 cm/s, which is considered an index of arteriosclerosis, BMI was the independent variable. When divided by 1963 cm/s, which is considered a mortality risk index, BMI, abnormal ankle reflex, and TRSC% were the independent variables.

Conclusion: Arteriosclerosis in patients with T2DM is associated with a decrease in lower limb circumference. TRSC% was independently associated with severe arteriosclerosis.

Key Words: arteriosclerosis, ba-PWV, body composition, diabetes mellitus

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Background

Type 2 diabetes mellitus (T2DM) causes vascular endothelial dysfunction. Additionally, patients with T2 DM present with clinically characterized early-onset and progressive hypertension accompanied by arteriosclerosis[1]. The duration of T2DM was independently associated with brachial-ankle pulse wave velocity (ba-PWV), even after adjusting for age, blood pressure, heart rate, cardiovascular events, and the presence of metabolic syndrome[2]. Furthermore, ba-PWV values in patients with T2DM increased with increasing plasma glucose levels and showed a significant positive correlation with waist circumference and the waist-hip ratio[3]. These findings suggest that the duration of T2 DM, body composition, and arteriosclerosis are closely related. Conversely, ba-PWV values were negatively correlated with appendicular skeletal muscle index and handgrip strength; therefore, ba-PWV was seen as a risk factor for sarcopenia[4]. Moreover, the progression of atherosclerosis as measured using ba-PWV values was found to predict the risk of all-cause and cause-specific mortality in T2DM, supporting the prognostic utility of ba-PWV[5].

In patients with T2DM, lower limb strength has been reportedly associated with the severity of peripheral neuropathy, wherein patients with peripheral neuropathy exhibit significantly lower ankle plantar flexor strength[6]. In a study, the percentage of slow-twitch fibers had decreased in patients with T2DM because of the high number of capillaries in slow-twitch fibers affected by atherosclerosis[7]. In other studies, it was found that the soleus muscle of patients with T2DM experienced higher oxidative stress[8] and that the oxygen extraction of the skeletal muscle was lower than in normal participants[9]. It can be inferred that arteriosclerosis and peripheral neuropathy lead to reduced lower limb strength and muscle atrophy in patients with T2DM.

Meanwhile, measuring the lower limb circumference is useful for screening for skeletal muscle atrophy and has recently been used to screen for sarcopenia. Because the lower limb circumference reflects the morphological factors of the soleus[10], patients with T2DM are expected to have reduced lower limb circumference due to prolonged morbidity or disease progression; however, the details are unclear. Additionally, lower limb circumference has also been significantly correlated with increased insulin resistance, which is known to cause angiopathy[11]. Insulin resistance is associated with decreased nitric oxide and endothelin-1 production, leading to vascular dysfunction[12], suggesting that reduced lower limb circumference may be related to the degree of arteriosclerosis progression.

Therefore, the purpose of this study was to determine the influence of body composition indices including lower extremity circumference, muscle strength, and patient characteristics on the progression of arterial stiffness in patients with T2DM. The progression of arteriosclerosis was determined by measuring ba-PWV, and related factors were investigated at the same time.

Methods

Study participants

A total of 128 patients with stable symptoms of diabetes mellitus who indicated their willingness to participate in the open call conducted during the study period were evaluated. The exclusion criteria were: type 1 diabetes mellitus, lower limb motor disorders (not excluded in the absence of edema or swelling of the lower limb), missing limbs, obvious paralysis due to central nervous system disorder, ankle-brachial pressure index (ABI) of ≤0.9, suspected lower limb arterial occlusion, malignant neoplasms, pregnancy or suspected pregnancy, internal implants such as a cardiac pacemaker, severe edema of the lower limbs, and any other patients deemed ineligible to participate by the attending physician. This excluded 14 patients, and thus, 114 patients were included in the analysis. The corresponding flowchart of patient inclusion in the cross-sectional study is shown in Fig. 1. Data were collected from medical records on the patient characteristics such as age, duration of T2DM, height, body weight, HbA1c, blood glucose level, and triglycerides. The purpose of the study was explained to the participants, and verbal and written consent were obtained. Participants who provided consent were included in the study. This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Dokkyo Medical University (approval number: Nikko

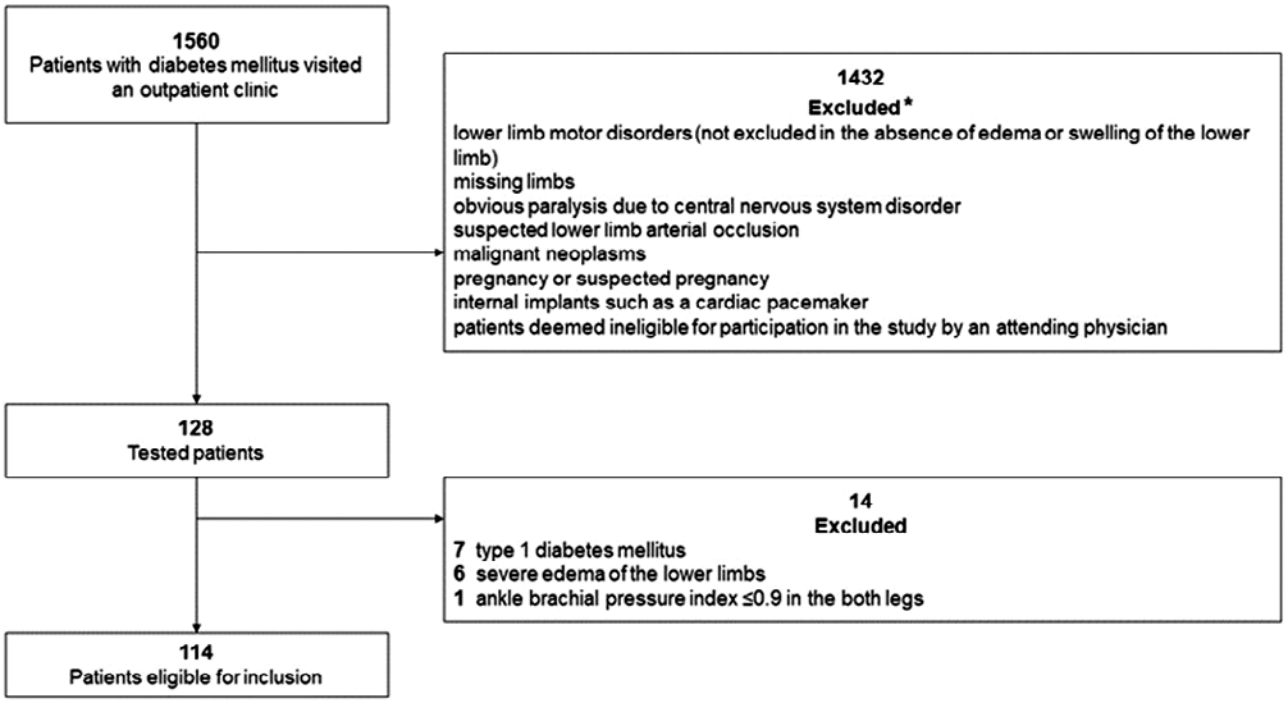

Figure 1 Flow chart of patient inclusion in the cross-sectional study.
The exclusion criteria were: patients with type 1 diabetes mellitus, lower limb motor disorders (not excluded in the absence of edema or swelling of the lower limb), missing limbs, obvious paralysis due to central nervous system disorder, ankle-brachial pressure index (ABI) of ≤ 0.9, suspected lower limb arterial occlusion, malignant neoplasms, pregnancy or suspected pregnancy, internal implants such as a cardiac pacemaker, severe edema of the lower limbs, and any other patients deemed ineligible for participation in the study by an attending physician. This excluded 14 patients; thus, 114 patients were included in the analysis.

30015, Recognition date: July 10, 2020).

Body composition

Lower limb circumference measurement and bioelectrical impedance analysis (BIA) were performed. BIA was performed using a body composition meter (DC-430A-P, TANITA, Tokyo, Japan) to measure skeletal muscle mass, fat mass, and estimated bone mass. Body mass index (BMI) was calculated using the body height squared divided by the body weight. The corrected lean body mass and fat mass were obtained by dividing the skeletal muscle mass and fat mass, respectively, by body weight. Thigh circumference (measured at 50% and at the distal 75% of the femur length) and lower limb circumference (measured over the tibial tuberosity and on the calf at the proximal 26% of the fibula) were measured with the patient in a supine position using a tape measure. The lower limb circumference was measured in units of 1 mm. To measure the calf circumference at the proximal 26% of the fibula, the length of the lower limb was considered 100%, and the maximum calf circumference was measured at 26% of the length from the fibular head[10]. As the lower limb circumference typically varies by physique and sex, the circumference measured at 50% and at the distal 75% of the femur length were corrected by dividing their measurements by the circumference at the tibial tuberosity. Further, the circumference measured at 50% and at the distal 75% of the femur length were corrected by dividing their measurements by the calf circumference at the proximal 26% of the fibula. The percentage ratio of the circumference at the tibial tuberosity to the maximum circumference of the lower leg (TRSC%: Circumferential diameter of tibial rough surface / Circumferential diameter of tibia, at the calf at the proximal 26% of the fibula) was also calculated. These corrections were made to compensate for individual variations in height and weight. Fig. 2 shows the measurement points and methods used to correct the lower limb circumference.

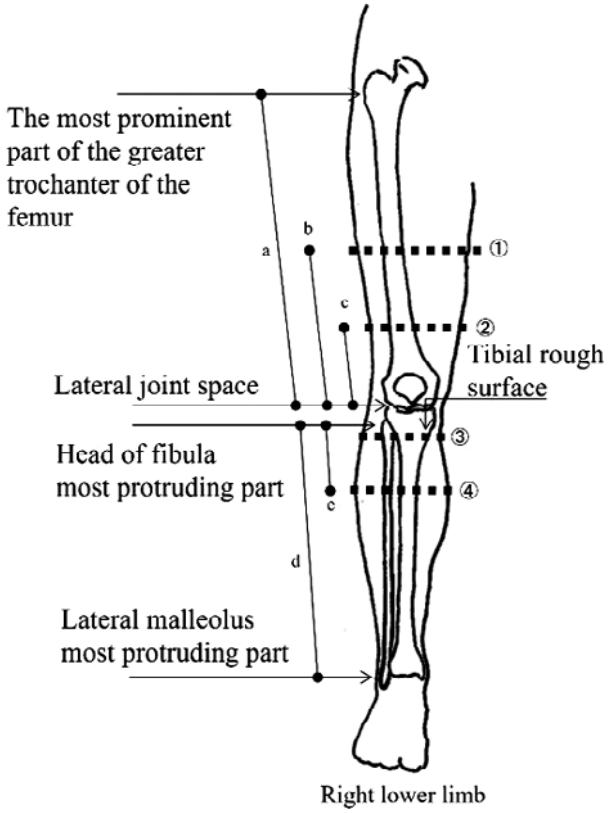

Figure 2 Measurement points and correction methods for lower limb circumference.

Measurement point. **a**: Distance between the most prominent part of the greater trochanter of the femur and lateral joint space; **b**: Half the length of "a" **c**: 1/4 the length of "a," **d**: Distance between the most protruding part of the head of the fibula and the most protruding part of the lateral malleolus. **e**: 26% the length of "d." Dotted line: The location where the circumference was measured. Name of the measurement point. ①: Femur circumference measured at 50% of the femur length ②: Femur circumference measured at the distal 75% of the femur length; ③: Circumference at the tibial tuberosity ④: Maximum calf circumference (measured at the calf at the proximal 26% of the fibula). Correction method (name = correction formula) Maximum calf circumference-Femur circumference at the distal 75% (%) = ④/① × 100. Maximum calf circumference -Femur circumference at 50% (%) = ④/② × 100. Percentage ratio of the femur circumference at 50% to the tibial tuberosity circumference (%) = ①/③ × 100. Percentage ratio of the femur circumference at the distal 75% to the tibial tuberosity circumference (%) = ②/③ × 100. Percentage ratio of the maximum calf circumference to the tibial tuberosity circumference (%) = ④/③ × 100

Muscle strength indicators

The strength of the knee extensors and ankle plantar flexors was measured in the sitting position using a handheld dynamometer (μ-tas MT1; ANIMA Co., Tokyo, Japan). Knee extension muscle strength and ankle plantar flexion muscle strength were calculated as the product of the value obtained by the handheld dynamometer (Nm) and lower leg length (m) and then divided by muscle mass (kg) and body weight (kg), respectively, to correct for body size[13]. The grip strength of the dominant hand was measured using a standard digital grip dynamometer (Grip-D; Takei Scientific Instruments Co., Ltd., Niigata, Japan). Measurements were taken twice while the patient was sitting, with the arm positioned perpendicular to the ground. The participants were instructed to adjust the handle of the dynamometer so that it would be under the second phalanx when gripped. The mean values of all measurements were used for analysis.

Arteriosclerosis indicators

ABI, systolic BP, and ba-PWV were measured using a blood pressure pulse wave measurement device (HBP-8000, Fukuda Colin Co., Ltd., Tokyo, Japan) after resting in the supine position for at least 10 minutes in an air-conditioned room (temperature approximately 26° C). It was ensured that the patient had not taken any medication, consumed alcohol, smoked, eaten, or drank within 2 hours prior to the measurement.

Diagnosis of clinical diabetic neuropathy

The assessment was performed under two preconditions and three neurological examination items. The preconditions were (1) being diagnosed with diabetes and (2) exclusion based on neurological disorders, except for diabetic peripheral neuropathy (DPN). DPN was considered if two or more of the following criteria were present: (1) symptoms believed to be caused by DPN, (2) reduced vibration thresholds at the bilateral medial malleolus, and (3) decrease in or disappearance of the bilateral Achilles tendon reflex[14]. To measure the vibration threshold of the bilateral medial malleolus, the patient was placed on his back on the treatment bed and the time from the start of the measurement until no vibration was felt in the bilateral endocardium was measured using a 128 Hz tuning fork. The patient was considered positive if the vibration sensing time was within 10 seconds.

Table 1 Patient characteristics.

Patient characteristics	Group	All (n = 114)	Male (n = 69)	Female (n = 45)	P-value (Male vs. Female)
Age (years)	-	63.12 ± 11.96	61.19 ± 11.63	66.09 ± 11.99	**0.032**
Duration of T2DM (years)	-	11.245 ± 9.451	11.77 ± 9.91	10.44 ± 8.75	0.467
Height (m)	-	1.62 ± 0.09	1.67 ± 0.06	1.54 ± 0.06	**< 0.001**
Body weight (kg)	-	67.46 ± 14.93	71.85 ± 13.18	60.72 ± 15.07	**< 0.001**
HbA1c (%) [Minimum value, maximum value]	-	6.80 [5.50, 9.20]	6.80 [5.50, 9.20]	6.80 [5.60, 8.70]	0.440
Blood glucose level (mg/dL)	-	153.40 ± 51.54	140.98 ± 38.83	161.51 ± 57.18	**0.037**
Triglyceride (mg/dL)	-	158.43 ± 120.06	155.87 ± 107.49	162.36 ± 138.33	0.779
HDL cholesterol (mg/dL)	-	57.37 ± 14.47	59.98 ± 15.97	55.73 ± 13.30	0.137
LDL cholesterol (mg/dL)	-	105.06 ± 33.48	102.00 ± 25.12	107.70 ± 39.56	0.53
T-cholesterol (mg/dL)	-	198.86 ± 36.12	210.94 ± 28.50	194.02 ± 38.00	0.114
COPD (%)	Applicable	1 (0.9)	1 (1.4)	0 (0.0)	1
	Not applicable	113 (99.1)	68 (98.6)	45 (100.0)	
Hepatitis C (%)	Applicable	1 (0.9)	1 (1.4)	0 (0.0)	1
	Not applicable	113 (99.1)	68 (98.6)	45 (100.0)	
Hypertension (%)	Applicable	77 (67.5)	44 (63.8)	33 (73.3)	0.313
	Not applicable	37 (32.5)	25 (36.2)	12 (26.7)	
Epilepsy (%)	Applicable	1 (0.9)	0 (0.0)	1 (2.2)	0.395
	Not applicable	113 (99.1)	69 (100.0)	44 (97.8)	
Graves' disease (%)	Applicable	4 (3.5)	1 (1.4)	3 (6.7)	0.299
	Not applicable	110 (96.5)	68 (98.6)	42 (93.3)	
Ischemic Heart Disease (%)	Applicable	11 (9.6)	6 (8.7)	5 (11.1)	0.75
	Not applicable	103 (90.4)	63 (91.3)	40 (88.9)	
Cerebrovascular disease (%)	Applicable	9 (7.9)	4 (5.8)	5 (11.1)	0.314
	Not applicable	105 (92.1)	65 (94.2)	40 (88.9)	
Hashimoto's thyroiditis (%)	Applicable	2 (1.8)	1 (1.4)	1 (2.2)	1
	Not applicable	112 (98.2)	68 (98.6)	44 (97.8)	
Hypothyroidism (%)	Applicable	4 (3.5)	4 (5.8)	0 (0.0)	0.152
	Not applicable	110 (96.5)	65 (94.2)	45 (100.0)	
Hypercholesterolemia (%)	Applicable	59 (51.8)	31 (44.9)	28 (62.2)	0.086
	Not applicable	55 (48.2)	38 (55.1)	17 (37.8)	
Dyslipidemia (%)	Applicable	17 (14.9)	11 (15.9)	6 (13.3)	0.792
	Not applicable	97 (85.1)	58 (84.1)	39 (86.7)	
Hyperuricemia (%)	Applicable	12 (10.5)	10 (14.5)	2 (4.4)	0.121
	Not applicable	102 (89.5)	59 (85.5)	43 (95.6)	
Osteoporosis (%)	Applicable	5 (4.4)	1 (1.4)	4 (8.9)	0.078
	Not applicable	109 (95.6)	68 (98.6)	41 (91.1)	
Fatty liver (%)	Applicable	1 (0.9)	1 (1.4)	0 (0.0)	1
	Not applicable	113 (99.1)	68 (98.6)	45 (100.0)	
Chronic hepatitis (%)	Applicable	12 (10.5)	7 (10.1)	5 (11.1)	1
	Not applicable	102 (89.5)	62 (89.9)	40 (88.9)	
Chronic cardiac insufficiency (%)	Applicable	1 (0.9)	0 (0.0)	1 (2.2)	0.395
	Not applicable	113 (99.1)	69 (100.0)	44 (97.8)	
Chronic renal insufficiency (%)	Applicable	1 (0.9)	1 (1.4)	0 (0.0)	1
	Not applicable	113 (99.1)	68 (98.6)	45 (100.0)	

Neuropathy	Group	All (n = 114)	Male (n = 69)	Female (n = 45)	P-value (Male vs. Female)
Abnormal ankle reflex (%)	Applicable	59 (51.8)	33 (47.8)	26 (57.8)	0.341
	Not applicable	55 (48.2)	36 (52.2)	19 (42.2)	
Probable neuropathy (%)	Applicable	97 (85.1)	55 (79.7)	42 (93.3)	0.060

Table 1 Patient characteristics. (continued)

Decreased vibration perception (%)	Not applicable	17 (14.9)	14 (20.3)	3 (6.7)	0.690
	Applicable	40 (35.1)	23 (33.3)	17 (37.8)	
Number of neuropathy findings (%)	Not applicable	74 (64.9)	46 (66.7)	28 (62.2)	0.425
	one	33 (28.9)	18 (26.1)	15 (33.3)	
	two	27 (23.7)	15 (21.7)	12 (26.7)	
	three	43 (37.7)	27 (39.1)	16 (35.6)	
	four	11 (9.6)	9 (13.0)	2 (4.4)	
Sensory symptoms (%)	Applicable	45 (39.5)	24 (34.8)	21 (46.7)	0.242
	Not applicable	69 (60.5)	45 (65.2)	24 (53.3)	

Body composition and muscle strength	Group	All (n = 114)	Male (n = 69)	Female (n = 45)	P-value (Male vs. Female)
BMI (kg/m^2)	-	25.58 ± 4.35	25.65 ± 3.85	25.46 ± 5.05	0.821
Skeletal muscle mass (kg)	-	44.61 ± 9.28	36.24 ± 5.07	50.08 ± 7.06	**< 0.001**
Skeletal muscle rate (kg/body weight)	-	0.67 ± 0.08	0.61 ± 0.07	0.7 ± 0.05	**< 0.001**
Estimated bone mass (kg)	-	2.54 ± 0.49	2.77 ± 0.36	2.2 ± 0.48	**< 0.001**
Fat mass (kg)	-	20.61 ± 8.92	19.48 ± 7.77	22.33 ± 10.29	0.095
Thigh circumference (measured at the distal 75% of the femur length) (cm)	-	40.24 ± 5.06	40.34 ± 4.3	40.08 ± 6.1	0.788
Thigh circumference (measured at 50% of the femur length) (cm)	-	46.65 ± 5.57	47.34 ± 5.02	45.59 ± 6.24	0.102
lower limb circumference (on the calf at the proximal 26% of the fibula) (cm)	-	36.01 ± 3.86	36.75 ± 3.56	34.87 ± 4.07	**0.010**
Calf 26% - Thigh circumference (measured at the distal 75% of the femur length) (%)	-	89.89 ± 6.14	91.35 ± 5.23	87.65 ± 6.78	**0.001**
Calf 26% - Thigh circumference (measured at 50% of the femur length) (%)	-	77.43 ± 4.68	77.8 ± 3.95	76.87 ± 5.62	0.300
Tibial rough surface- Thigh circumference (measured at the distal 75% of the femur length) (%)	-	119.31 ± 10.02	118.21 ± 7.29	121 ± 13.06	0.146
Tibial rough surface- Thigh circumference (measured at 50% of the femur length) (%)	-	138.28 ± 9.13	138.72 ± 8.44	137.6 ± 10.16	0.523
TRSC% (%)	-	106.78 ± 5.24	107.72 ± 5.1	105.34 ± 5.17	**0.017**
Grip strength (kg/body)	-	0.45 ± 0.13	0.5 ± 0.11	0.37 ± 0.1	**< 0.001**
Knee extension muscle strength (Nm/kg/body weight)	-	14 ± 4.16	15.83 ± 3.86	11.19 ± 2.82	**< 0.001**
Knee extension moment (Nm)	-	3.68 ± 2.29	4.11 ± 2.56	3.01 ± 1.6	**0.012**
Ankle extension muscle strength (Nm/kg/body weight)	-	22.24 ± 10.74	25.91 ± 11	16.63 ± 7.46	**< 0.001**
Ankle extension moment (Nm)	-	4.32 ± 4.97	4.73 ± 5.49	3.7 ± 4.02	0.278

Table 1 Patient characteristics. (continued)

Arteriosclerosis Indicators	Group	All (n = 114)	Male (n = 69)	Female (n = 45)	P-value (Male vs. Female)
Brachial-ankle PWV (cm/s)	-	1666.03 ± 368.19	1629.51 ± 374.17	1722.02 ± 355.65	0.191
Ankle-brachial index	-	1.12 ± 0.08	1.13 ± 0.08	1.11 ± 0.09	0.352
Systolic BP (mmHg)	-	139.36 ± 16.52	135.96 ± 13.69	144.58 ± 19.12	**0.006**

The data is the mean ± SD or median (%) of variables with a biased distribution. "Muscle strength" is the strength per unit of body weight and even per unit of total muscle mass. Bold values indicate statistical significance ($p < 0.05$)

t-test, X^2 test. HDL High-density lipoprotein, LDL Low-Density Lipoprotein, T-cholesterol Total cholesterol, baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; T2DM, type 2 diabetes mellitus; TRSC%, tibial rough surface - calf 26%; BP, blood pressure; COPD, chronic obstructive pulmonary disease.

Calf 26%-Femur 25% (%) = calf 26% position circumference/femur 50% position circumference × 100

Calf 26%-Femur 50% (%) = calf 26% position circumference/femur 25% position circumference × 100

Tibial rough surface-Femur 50% (%) = femur 50% position circumference/tibial rough surface position circumference × 100

Tibial rough surface-Femur 25% (%) = femur 25% position circumference/tibial rough surface position circumference × 100

Tibial rough surface-calf 26% (%) = calf 26% position circumference/tibial rough surface position circumference × 100

Table 2 Medication information.

Medication	All (n = 114)	Male (n = 69)	Female (n = 45)
	n (%)	n (%)	n (%)
DPP4 inhibitor	57 (50)	37 (53.6)	20 (44.4)
Alpha glucosidase inhibitor	51 (44.7)	38 (55.1)	13 (28.9)
Biguanide (metformin)	38 (33.3)	27 (39.1)	11 (24.4)
SGLT2 inhibitor	25 (21.9)	18 (26.1)	7 (15.6)
Insulin	20 (17.5)	18 (26.1)	2 (4.4)
GLP1 agonist (injection)	11 (9.6)	7 (10.1)	4 (8.9)
Rapid-acting insulin secretagogue (Glinide)	8 (7.0)	3 (4.3)	5 (11.1)
SU	6 (5.3)	4 (5.8)	2 (4.4)
Statins	59 (51.7)	29 (42.0)	30 (66.7)
Non-Statin Hyperlipidemic Agents	19 (16.7)	12 (17.4)	7 (15.6)
ARB	53 (46.5)	30 (43.5)	23 (51.1)
CCB	53 (46.5)	33 (47.8)	20 (44.4)
ACE-I	3 (2.6)	2 (2.9)	1 (2.2)
Other antihypertensive drugs	14 (12.3)	9 (13.0)	5 (11.1)

DPP-4: dipeptidyl peptidase-4

SGLT-2: sodium glucose cotransporter-2

GLP1: Glucagon-like peptide-1

SU: Sulfonylurea

ARB: angiotensin receptor blocker

CCB: calcium channel blocker

ACE-I: angiotensin converting enzyme inhibitor

Statistical analysis

To examine the associations between ba-PWV and the examination values, Pearson's product rate correlation coefficient test was used for parametric data, and Spearman's rank correlation coefficient test was used for nonparametric data. To identify factors that influence ba-PWV values, ba-PWV was used as the dependent variable in the multiple regression analysis (stepwise variable selection using Bayesian information criterion). The independent variables were TRSC%, which was a factor in simple regression analysis, duration of T2DM in years[15], abnormal ankle reflex[16], and

Table 3 Simple regression analysis of baPWV.

	Estimate	95% CI	t-value	p-value
Age (years)	0.569	0.43-0.682	7.327	**< 0.001**
Duration of T2DM (years)	0.213	0.03-0.382	2.310	**0.023**
Sex	-0.147	-0.322-0.038	-1.575	0.118
Height (m)	-0.261	-0.424-0.08	-2.855	**0.005**
Body weight (kg)	-0.475	-0.606-0.319	-5.710	**< 0.001**
HbA1c (%)	0.181	-0.003-0.353	1.952	0.053
Blood glucose level (mg/dL)	0.322	0.147-0.478	3.604	**< 0.001**
Triglyceride (mg/dL)	-0.068	-0.249-0.117	-0.721	**< 0.001**
HDL cholesterol (mg/dL)	0.080	-0.11-0.264	0.828	0.409
LDL cholesterol (mg/dL)	0.259	-0.488-0.005	-1.967	0.054
T-cholesterol (mg/dL)	0.212	-0.0539-0.45	1.590	0.117
Abnormal ankle reflex	0.206	0.023-0.375	2.224	**0.028**
Probable neuropathy	0.034	-0.151-0.217	0.361	0.719
Decreased vibration perception	0.137	-0.048-0.313	1.465	0.146
Number of neuropathy findings	0.158	-0.026-0.333	1.697	0.092
Sensory symptoms	-0.062	-0.243-0.123	-0.659	0.511
BMI (kg/m^2)	-0.446	-0.582-0.285	-0.685	0.495
Skeletal muscle mass (kg)	-0.346	-0.498-0.173	-3.903	**< 0.001**
Skeletal muscle rate (kg/body weight)	0.256	0.075-0.42	2.797	**0.006**
Estimated bone mass (kg)	-0.411	-0.553-0.246	-4.775	**< 0.001**
Fat mass (kg)	-0.426	-0.565-0.262	-4.980	**< 0.001**
Thigh circumference (measured at the distal 75% of the femur length) (cm)	-0.381	-0.528-0.212	-4.364	**< 0.001**
Thigh circumference (measured at 50% of the femur length) (cm)	-0.483	-0.613-0.328	-5.839	**< 0.001**
lower limb circumference (on the calf at the proximal 26% of the fibula) (cm)	-0.516	-0.639-0.367	-6.376	**< 0.001**
Calf 26%-Thigh circumference (measured at the distal 75% of the femur length) (%)	-0.414	-0.556-0.249	-4.811	**< 0.001**
Calf 26%-Thigh circumference (measured at 50% of the femur length) (%)	-0.212	-0.381-0.029	-2.291	**0.024**
Tibial rough surface-Thigh circumference (measured at the distal 75% of the femur length) (%)	-0.101	-0.28-0.084	-1.078	0.284
Tibial rough surface-Thigh circumference (measured at 50% of the femur length) (%)	0.034	-0.151-0.217	0.363	0.718
TRSC% (%)	-0.522	-0.644-0.374	-6.470	**< 0.001**
Grip strength (kg/body)	0.045	-0.14-0.227	0.475	0.636
Knee extension muscle strength (Nm/kg/body weight)	-0.210	-0.379-0.027	-2.272	**0.025**
Knee extension moment (Nm)	-0.117	-0.294-0.069	-1.242	0.217
Ankle extension muscle strength (Nm/kg/body weight)	-0.046	-0.228-0.139	-0.489	0.626
Ankle extension moment (Nm)	-0.031	-0.213-0.154	-0.324	0.747
Ankle brachial index	0.264	0.084-0.427	2.899	**0.005**
Systolic BP (mmHg)	0.542	0.398-0.66	6.830	**< 0.001**

The data is the mean ± SD or median (interquartile range) of variables with a biased distribution or percentage.

"Muscle strength" is the strength per unit of body weight and even per unit of total muscle mass.

Bold values indicate statistical significance ($p < 0.05$)

HDL High-density lipoprotein, LDL Low-Density Lipoprotein, T-cholesterol Total cholesterol, baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; T2DM, type 2 diabetes mellitus; TRSC%, tibial rough surface-calf 26%; BP, blood pressure

Estimates are expressed with r for parametric data and ρ for non-parametric data.

T2DM Type 2 diabetes, BP blood pressure, CI Confidence interval

Calf 26%-Femur 25% (%) = Calf 26% position circumference/Femur 50% position circumference × 100

Calf 26%-Femur 50% (%) = Calf 26% position circumference/Femur 25% position circumference × 100

Tibial rough surface-Femur 50% (%) = Femur 50% position circumference/Tibial rough surface position circumference × 100

Tibial rough surface-Femur 25% (%) = Femur 25% position circumference/Tibial rough surface position circumference × 100

Tibial rough surface-calf 26% (%) = Calf 26% position circumference/Tibial rough surface position circumference × 100

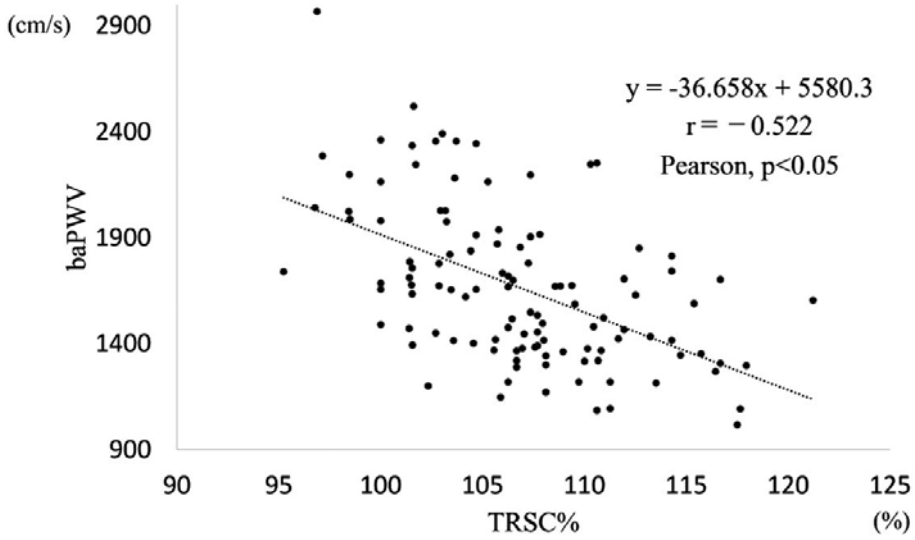

Figure 3 Relationship between ba-PWV and TRSC%.
ba-PWV: Brachial-ankle pulse wave velocity. TRSC%: Tibial rough surface-calf 26%

grip strength weight ratio (kg/body weight)[17], which were factors in simple regression and previous studies; and BMI (kg/m^2)[18], HbA1c (%)[19], and sex[20] which are generally associated with diabetic complications. These factors were adjusted for age (years)[15,18,19] and systolic BP (mmHg)[15,18,19]. In addition, ba-PWV was categorized at 1400 cm/s (arteriosclerosis indicator), 1650 cm/s (cardiovascular risk indicator), and 1963 cm/s (mortality risk indicator) based on previous studies[21-23] to perform binomial logistic regression with the same independent variables and adjustment variables used in the multiple regression analysis. Multiple regression analysis and logistic regression were checked for multicollinearity and those with a Variance Inflation Factor (VIF) < 5.0 were assumed to be free of multicollinearity. The normality of all variables was confirmed in advance using Q-Q plots and the Shapiro-Wilk normality test. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[24]. Statistical significance was set at $p < 0.05$ two-tailed.

Results

The clinical characteristics of the 114 patients are presented in Table 1, 2.

In the simple regression analyses, correlations with ba-PWV were observed for age (years) ($r = 0.569$, $p < 0.001$), duration of T2DM (years) ($r = 0.213$, $p < 0.023$), height (m) ($r = -0.261$), $p < 0.005$), body weight (kg) ($r = -0.475$, $p < 0.001$), blood glucose level (mg/dl) ($r = 0.322$, $p < 0.001$), triglyceride (mg/dl) ($r = -0.0680$, $p < 0.001$), abnormal ankle reflex ($\rho = 0.206$, $p < 0.028$), skeletal muscle mass (kg) ($r = -0.3460$, $p < 0.001$), skeletal muscle rate (kg/body weight) ($r = 0.256$), $p < 0.006$), estimated bone mass (kg) ($r = -0.411$, $p < 0.001$), fat mass (kg) ($r = -0.426$, $p < 0.001$), femur 25% position circumference (cm) ($r = -0.381$, $p < 0.001$), femur 50% position circumference (cm) ($r = -0.483$, $p < 0.001$), calf 26% position circumference (cm) ($r = -0.516$, $p < 0.001$), calf 26%-femur 25% (%) ($r = -0.414$, $p < 0.001$), calf 26%-femur 50% (%) ($r = -0.217$, $p < 0.024$), TRSC% ($r = -0.522$, $p < 0.001$), knee extension muscle strength (Nm/kg/body weight) ($r = -0.210$, $p < 0.025$), ABI ($r = 0.264$, $p < 0.005$), and systolic BP (mmHg) ($r = 0.542$, $p < 0.001$) (Table 3).

TRCS% had the strongest correlation with ba-PWV and lower limb circumferences (Fig. 3). BMI (m^2/kg) ($\beta = -0.244$, $p < 0.002$), HbA1c (%) ($\beta = 0.147$, $p < 0.022$), abnormal ankle reflex ($\beta = 0.148$, $p < 0.021$), and TRSC% ($\beta = -0.176$, p DKMJF010503.eps.026) were adopted as variables for multiple regression analysis with ba-PWV adjusted for age and blood pressure as the dependent variables. The multiple R^2 was 0.592, and the adjusted R^2 was 0.570 (Table 4). Logistic re-

Table 4 Multiple linear regression analysis of baPWV and each index.

	Univariate analysis				Multivariate				
	Estimate	Std. Error	t-value	p-value	Estimate	Std. Error	t-value	p-value	β
BMI (kg/m²)	-37.771	7.166	-5.271	**p < 0.001**	-20.668	6.361	-3.249	**0.002**	-0.244
HbA1c (%)	92.476	47.386	1.952	0.053	74.859	32.395	2.311	**0.023**	0.147
Duration of T2DM (years)	8.306	3.596	2.310	**0.023**					
Abnormal ankle reflex	180.909	67.178	2.693	**0.008**	108.216	46.305	2.337	**0.021**	0.148
Grip strength (kg/body weight)	130.488	274.718	0.475	0.636					
TRSC%	-36.658	5.666	-6.470	**p < 0.001**	-12.371	5.489	-2.254	**0.026**	-0.176
Sex	-92.515	70.323	-1.316	0.191					

Bold values indicate statistical significance ($p < 0.05$)

baPWV brachial-ankle pulse wave velocity; BMI, body mass index; T2DM, type 2 diabetes mellitus; TRSC%, tibial rough surface-calf 26%

Multiple R-squared: 0.592, Adjusted R-squared: 0.570

p-value: < 0.001

Adjustment for age, systolic blood pressure.

TRSC% Tibial rough surface-calf 26%, β: adjusted coefficient

gression analysis was performed with ba-PWV categorized at 1400 cm/s, 1650 cm/s, and 1963 cm/s as the dependent variables and the same independent and adjustment variables as in the multiple regression analysis. At 1400 cm/s, BMI (m²/kg) (odds ratio [OR] 0.837, 95% confidence interval [CI] 0.726-0.965, $p < 0.05$) was selected. At 1963 cm/s, BMI (m²/kg) (OR 0.630, 95% CI 0.432-0.917, $p < 0.05$), abnormal ankle reflex (OR 34.0, 95% CI 3.38-342, $p < 0.01$), and TRSC% (OR 0.677, 95% CI, 0.508-0.902, $p < 0.01$) were selected (Table 5). No multicollinearity was observed in the results of multiple regression analysis and logistic regression.

Discussion

This study was undertaken to determine the effects of body composition indices, including lower extremity circumference, muscle strength, and patient characteristics on the progression of atherosclerosis in patients with T2DM. This is the first study to demonstrate that lower limb circumference is associated with increased ba-PWV values in patients with T2DM. In the simple regression analyses, correlations were observed with patient characteristics except for sex, laboratory data, some peripheral neuropathy findings, body composition indicators except for BMI, some lower limb circumference measurements, knee extension strength, and an arteriosclerosis indicator. Significant associations were also observed with BMI, HbA1c, abnormal ankle reflex, and TRSC%, even after adjusting for age and systolic blood pressure. In addition, logistic regression analyses of three ba-PWV levels selected TRSC% with more advanced arteriosclerosis, thus indicating that there is a relationship between arteriosclerosis and lower limb circumference in patients with T2DM.

In the multiple regression analysis, the β value, which indicates the effect of the independent variable on ba-PWV, showed that out of six factors, including the adjustment variables, TRSC% had the 4th highest degree of influence after SBP, age, and BMI. This was more influential than HbA1c and abnormal ankle reflex in this study. In our study, the association between HbA1c level and baPWV was low. This is consistent with the results of previous studies. One factor is that atherosclerosis is caused by hyperglycemia, but HbA1c does not necessarily reflect hyperglycemia[25]. In a systematic review of the literature, most reports found no association between sarcopenia and HbA1c in T2DM[26]. In a study of 102 patients diagnosed with diabetic polyneuropathy, arterial stiffness was predominantly worsened in the group that showed abnormal sensory nerve action potentials in the peroneal nerve[27]. In addition, a study of 733 patients with T2DM without cardiac disease[28] reported that BMI was negatively associated with ba-PWV even after adjustment for age and blood pressure. Furthermore, in a study of 54 patients with T2DM, baPWV was reported to be associated

Table 5 Binomial logistic regression analysis by degree of arteriosclerosis progression.

Separated by baPWV 1400 cm/s	Univariate analysis			Multivariate		
	Odds ratio	95% CI	p-value †	Odds ratio	95% CI	p-value †
BMI (kg/m²)	0.828	0.746 - 0.918	**p < 0.001**	0.837	0.726 - 0.965	0.014
HbA1c (%)	1.440	0.814 - 2.55	0.210			
Duration of T2DM (years)	1.050	0.998 - 1.1	**0.060**			
Abnormal ankle reflex	1.560	0.712 - 3.41	0.267			
Grip strength weight ratio (kg/body weight)	14.200	0.572 - 351	0.106			
TRSC%	0.837	0.765 - 0.917	**p < 0.001**			
Sex	0.672	0.3 - 1.51	0.335			

Separated by baPWV 1650 cm/s	Univariate analysis			Multivariate		
	Odds ratio	95% CI	p-value †	Odds ratio	95% CI	p-value †
BMI (kg/m²)	0.827	0.744 - 0.919	**p < 0.001**			
HbA1c (%)	1.630	0.952 - 2.79	0.075			
Duration of T2DM (years)	1.030	0.986 - 1.07	0.206			
Abnormal ankle reflex	2.030	0.962 - 4.28	0.063			
Grip strength weight ratio (kg/body weight)	2.790	0.149 - 52.4	0.492			
TRSC%	0.797	0.721 - 0.881	**p < 0.001**			
Sex	0.653	0.307 - 1.39	0.268			

Separated by baPWV 1963 cm/s	Univariate analysis			Multivariate		
	Odds ratio	95% CI	p-value †	Odds ratio	95% CI	p-value †
BMI (kg/m²)	0.729	0.616 - 0.861	**p < 0.001**	0.630	0.432 - 0.917	**0.016**
HbA1c (%)	1.400	0.765 - 2.56	0.276			
Duration of T2DM (years)	1.040	0.995 - 1.09	0.083			
Abnormal ankle reflex	3.320	1.25 - 8.81	**0.016**	34.000	3.38 - 342	**0.003**
Grip strength weight ratio (kg/body weight)	0.436	0.0119 - 16	0.651			
TRSC%	0.724	0.624 - 0.839	**p < 0.001**	0.677	0.508 - 0.902	**0.008**
Sex	0.375	0.149 - 0.942	0.037			

Bold values indicate statistical significance ($p < 0.05$)

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; T2DM, type 2 diabetes mellitus; TRSC%, tibial rough surface-calf 26%

† Binary logistic regression analysis

Adjustment for age, systolic blood pressure.

CI: confidence interval

with systolic blood pressure[29]. Our results support these findings. We also found that ba-PWV was associated with TRSC%.

Moreover, for the correlations between ba-PWV and lower limb circumferences, the correlation coefficients were higher for values related to maximum lower limb circumference than for those related to thigh circumference, with TRSC% being the highest. Lower limb circumference is also used as an indicator of sarcopenia[30], and sarcopenia is a risk factor for arteriosclerosis[31]. A decline in muscle mass has been reported to reduce anti-inflammatory myokine secretion and cause arteriosclerosis[32]. Lower limb circumference can be used to assess reduced muscle mass, which is considered to be associated with arteriosclerosis. The strong correlation between lower limb circumference and thigh circumference can be attributed to the significantly higher oxidization rate in the soleus of patients with DM than in young and healthy older adult patients[8]. Furthermore, as the lower limb muscles are pe-

ripheral sites, microangiopathies accompanying circulatory disorders in patients with DM have a particularly large impact on them.

In the logistic regression analyses, TRSC% was selected when arteriosclerosis was more advanced. A previous study reported an association between homeostasis model assessment-insulin resistance (HOMA-IR), an indicator of the progression of T2DM, and lower limb circumference and found that HOMA-IR was associated with carotid intima-media thickness[11]. This can be interpreted as worsening of arteriosclerosis as T2DM progresses, and it is surmised that the TRSC% decline and arteriosclerosis progression occur in parallel, suggesting that increasing ba-PWV, or the progression of arteriosclerosis, can be evaluated by measuring the lower limb circumference to evaluate the decrease in lower limb muscle mass. In the present study, TRSC% had the fourth largest impact on ba-PWV after systolic BP, age, and BMI. This can be interpreted as worsening arteriosclerosis when muscular atrophy occurs in the lower limbs. Sarcopenia increases inflammation and may induce atherosclerosis[32,33]. This association between inflammation and atherosclerosis has been reported to be associated with baPWV, high-sensitivity C-reactive protein, and the neutrophil-lymphocyte ratio[34]. Therefore, it was determined that lower extremity muscle atrophy in this study also affects atherosclerosis.

The results of the present study also demonstrate the relationship between the progression of arteriosclerosis and lower limb muscle morphology in patients with DM, which indicates that lower limb circumference could be used to screen for arteriosclerosis in these patients. Arteriosclerosis can be easily evaluated using various specialized devices; however, it is difficult to assess without such specialized equipment. With TRSC%, it would be possible to perform these assessments outside the hospital environment, such as in nursing care settings or via telemedicine, without the need for specialized equipment. Demonstrating if a causative relationship exists in future studies could lead to its clinical application.

Limitations

Although we observed a relationship between lower limb circumference and the progression of arteriosclerosis in this study, the specific mechanism of this relationship, including the expression of inflammatory cytokines, remains unknown. In addition, although this study describes the relationship between leg circumference and insulin resistance, the participants of this study were patients visiting an outpatient clinic, and fasting plasma glucose, which is used to calculate HOMA-IR, could not be collected. Therefore, the relationship between leg circumference and insulin resistance has only been discussed based on the literature. Further, because this was a cross-sectional observational study, a prospective cohort study is needed to investigate changes in each factor, the effects of rehabilitation, and other areas.

Conclusion

In patients with T2DM, TRSC% was an independent factor of atherosclerosis. It was also an independent factor when the severity of arterial stiffness was classified as ba-PWV ≥ 1963 cm/s, an index of mortality risk. Thus, lower extremity circumference by TRSC% may reflect the progression of arterial stiffness.

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Disclosures

Author name TY has received contributions from AstraZeneca and Japan Abbott. Author TF, Author YT, Author HT, Author TT, Author SO, Author SK, Author TM, Author YN, declare that they have no conflicts of interest.

IRB information

This study was performed according to the principles of the Declaration of Helsinki and was approved by the institutional ethics committee of Dokkyo Medical University Nikko Medical Center

(approval number: Nikko 30015, Recognition date: July 10, 2020).

Constitution

There are 10 textpages. There are 3 figures and tables from Table 1 to Table 5.

Authors' contributions

TF carried out the design of the study and drafted the manuscript; YT and HT worked on giving advice and reviewing from a medical point of view; TT, SO, SK, TM, YN, and TY contributed to the discussion and revised the manuscript.

Informed Consent Statement

The purpose of the study was explained to the participants, and verbal and written consent was obtained. Participants who provided consent were included in the study.

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Conflict of interest

Author name TY has received contributions from AstraZeneca and Japan Abbott. Author TF, Author YT, Author HT, Author TT, Author SO, Author SK, Author TM, Author YN, declare that they have no conflicts of interest.

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