Relationship Between Arteriosclerosis and Body Composition in Patients with type 2 Diabetes Mellitus: Cross-Sectional Study

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Abstract

Background

Reduced lower limb circumference due to sarcopenia in patients with type 2 diabetes mellitus (T2DM) could be a useful screening tool for arteriosclerosis. Hence, the objective of this study was to clarify the relation between lower limb circumference and other body composition factors, muscle strength, and patient characteristics, and the progression of arteriosclerosis in patients with T2DM.

Methods

We included 114 patients with T2DM receiving outpatient care, and assessed body composition (lower limb circumferences including tibial rough surface-calf 26% [TRSC%]), muscle strength indicators, patient characteristics, clinical diabetic neuropathy status, and examined their associations with brachial–ankle pulse wave velocity (ba-PWV) using multiple regression analysis. Additionally, the severity of ba-PWV was classified into 1400 cm/s, 1650 cm/s, and 1963 cm/s to investigate their associations using logistic regression analysis.

Results

The mean age was 63.12±11.96 years and participants had T2DM for 11.25±9.45 years. Body mass index (BMI), HbA1c, abnormal ankle reflex, and TRSC% were adopted in the multiple regression analysis with ba-PWV as the dependent variable. In the logistic regression analysis of ba-PWV divided by 1400 cm/s, an index of arteriosclerosis, BMI was adopted, and when divided by 1963 cm/s, a mortality risk index, BMI, abnormal ankle reflex, and TRSC% were adopted.

Conclusion

Arteriosclerosis in patients with T2DM is associated with a decrease in lower limb circumference; TRSC% was independently associated with severe arteriosclerosis when ba-PWV was ≥1963 cm/s, which is an indicator of mortality risk. Thus, lower limb circumference in the form of TRSC% may reflect the progression of arteriosclerosis.

Background

Type 2 diabetes mellitus (T2DM) is a disease that causes vascular endothelial dysfunction. In addition, patients with T2DM present with hypertension, clinically characterized by young onset and progression, and 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 presence of metabolic syndrome [2]. In addition, ba-PWV in patients with T2DM increased along with plasma glucose levels and showed a significant positive correlation with waist circumference and waist–hip ratio [3]. These findings indicate that the duration of T2DM, body composition, and arteriosclerosis are closely related. Furthermore, the progression of atherosclerosis as measured by ba-PWV was found to predict the risk of all-cause and cause-specific mortality in T2DM, supporting the prognostic utility of ba-PWV [4].

Lower limb strength in patients with T2DM has been reported to be associated with the severity of peripheral neuropathy, with patients with T2DM who have peripheral neuropathy exhibiting significantly lower ankle
plantar flexor strength [5]. It has also been shown that red muscle fibers are susceptible to arteriosclerosis because they are rich in capillaries, and the soleus muscle of patients with T2DM exhibits higher levels of oxidative stress than healthy subjects [6]. In other words, arteriosclerosis and peripheral neuropathy leads to reduced lower limb strength and muscle atrophy in patients with T2DM.

Meanwhile, measuring lower limb circumference is useful for screening for skeletal muscle atrophy and has recently been used to screen for sarcopenia. Because lower limb circumference reflects the morphological factors of the soleus [7], patients with T2DM are expected to have reduced lower limb circumference due to prolonged morbidity or disease progression; however, the details are unclear. In addition, lower limb circumference has been found to be significantly correlated with increased insulin resistance, and insulin resistance is known to cause angiopathy [8], which suggests that reduced lower limb circumference may be related to the degree of arteriosclerosis progression.

Therefore, the objective of this study was to clarify the relation between lower limb circumference and other body composition factors, muscle strength, and patient characteristics, and the progression of arteriosclerosis in patients with T2DM. The progression of arteriosclerosis was determined by measuring ba-PWV, and the related factors were investigated.

**Methods**

**Study participants**

Patients with T2DM who visited the Kawatsuru Plaza Clinic and Motoyama Clinic from August 2019 to September 2020 were included in the study. We selected 128 patients who were capable of visiting the clinic independently and whose data were available on examination results and patient characteristics. 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 for participation in the study by an attending physician. This excluded 14 patients; thus, 114 patients were included in the analysis. Data were collected from medical records on the patient characteristics of 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 was 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 30015).

**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 evaluate skeletal muscle mass, fat mass, and estimated bone mass. Body mass index (BMI) was calculated from the height and weight measurements. The corrected lean body mass and fat mass were obtained by dividing the skeletal muscle
mass and fat mass, each, by body weight. Thigh circumference (femur 25% position circumference, femur 50% position circumference) and lower limb circumference (tibial rough surface position circumference, calf 26% position circumference) were measured with the patient in the supine position using a tape measure. Lower limb circumference was measured in units of 1 mm. To measure calf 26% position circumference, 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 [7]. As the lower limb circumference is expected to vary due to the effects of physique and sex, femur 25% position circumference, femur 50% position circumference, and calf 26% position circumference were corrected by dividing by the tibial rough surface position circumference. Further, the femur 25% position circumference and femur 50% position circumference were corrected by dividing by the calf 26% position circumference. TRSC% was obtained by correcting the calf's 26% position circumference by the tibial rough surface position circumference. Figure 1 shows the measurement points and methods used to correct the lower limb circumference.

**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 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 [9]. 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 in a sitting position, with the arm positioned horizontally 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).

**Diagnosis Of Clinical Diabetic Neuropathy**

The assessment was performed with two preconditions and three neurological examination items. The preconditions were (1) being diagnosed with diabetes and (2) ability to rule out neurological diseases other than diabetic peripheral neuropathy (DPN). DPN was considered in the presence of 2 or more of the following criteria: (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 [10].

**Statistical analysis**
Patient characteristics were compared by sex using an unpaired t-test. The $\chi^2$ test was used to compare the presence or absence of medical history factors and neurological symptoms. 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, ba-PWV was used as the dependent variable in the multiple regression analysis (stepwise variable selection using BIC). The independent variables were TRSC%, which was a factor in simple regression analysis, duration of T2DM (years) \[11\], abnormal ankle reflex \[12\], and grip strength weight ratio (kg/body weight) \[13\], which were factors in simple regression and previous studies; and BMI (m$^2$/kg) \[14\], HbA1c (%) \[15\], and sex\[16\] which are generally associated with diabetic complications. These factors were adjusted for age (years)\[11, 14, 15\] and systolic BP (mmHg) \[11, 14, 15\]. In addition, ba-PWV was separated at 1400 cm/s (arteriosclerosis indicator), 1650 cm/s (cardiovascular risk indicator), and 1963 cm/s (mortality risk indicator) based on previous studies \[17–19\]to perform binomial logistic regression with the same independent variables and adjustment variables used in the multiple regression analysis. 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), which is 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 \[20\]. Statistical significance was set at P < 0.05.

**Results**

The clinical characteristics of the 114 patients are presented in Table 1. The participants' age was 63.12 ± 11.96 years, height 1.62 ± 0.09 m, weight 67.46 ± 14.93 kg, and duration of T2DM was 11.25 ± 9.45 years. The participants had a history of hypertension (67.5%), hypercholesterolemia (51.8%), hyperlipidemia (14.9%), hyperuricemia (10.5%), chronic hepatitis (10.5%), ischemic heart disease (9.6%), ischemic cerebrovascular disorder (7.9%), osteoporosis (4.4%), Basedow disease (3.5%), hypothyroidism (3.5%), Hashimoto disease (1.8%), COPD (0.9%), hepatitis C (0.9%), epilepsy (0.9%), fatty liver (0.9%), chronic heart failure (0.9%), and chronic renal failure (0.9%), but no sex-based differences were observed. Additionally, no sex-based differences were observed for DPN or ba-PWV (Table 1).

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 2). TRCS% had the strongest correlation with ba-PWV and lower limb circumferences (Fig. 2). 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% ($\beta = -0.176, p < 0.026$) were adopted as variables for multiple regression analysis with ba-
PWV adjusted for age and blood pressure as the dependent variables. The multiple R-squared value was 0.592, and the adjusted R-squared was 0.570 (Table 3).

Logistic regression analysis was performed with ba-PWV separated 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% 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 4).

Discussion

This was the first study to demonstrate that lower limb circumference in patients with T2DM is associated with the progression of arteriosclerosis. 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, shows 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. BMI [14], HbA1c [15], systolic BP [14, 15], age [14, 15], and abnormal ankle reflex [12] have already been found to be related to ba-PWV. 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 [21], and sarcopenia is a risk factor for arteriosclerosis [22]. A decline in muscle mass has been reported to reduce anti-inflammatory myokine secretion and cause arteriosclerosis [23]. 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 oxidation rate in the soleus of DM patients than in young and healthy elderly subjects [6]. Furthermore, as muscles of the lower limb are peripheral sites, microangiopathies accompanying circulatory disorders in DM patients 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 (IMT) [8]. This can be interpreted as worsening of arteriosclerosis as T2DM progresses, and it is surmised that TRSC% declines and arteriosclerosis progress 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. As sarcopenia may increase inflammation and induce arteriosclerosis [23, 24], we conclude that lower limb muscle atrophy also has an impact on arteriosclerosis.

The results of the present study also demonstrate the relationship between the progression of microangiopathy and lower limb muscle morphology in DM patients, which indicates that lower limb circumference could possibly 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, with no need for specialized equipment. Demonstrating if a causative relationship exists in future studies could lead to its clinical applications.

**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. 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**

TRSC% was independently associated with arteriosclerosis in patients with T2DM. TRSC% was also an independent factor when the severity of arteriosclerosis was separated at ba-PWV \( \geq 1963 \) cm/s, which is an indicator of mortality risk. This indicates that lower limb circumference in the form of TRSC% may reflect the progression of arteriosclerosis.

**Abbreviations**

- HDL: High density lipoprotein
- LDL: Low Density Lipoprotein
- T-Cho: Total cholesterol
- ba-PWV: brachial–ankle pulse wave velocity
- BMI: body mass index
- BP: blood pressure
CI: confidence interval

cm : centimeter

s : seconds

DM: diabetes mellitus

dpn : diabetic peripheral neuropathy

kg : kilogram

m : meter

mg/dl : milligram/deciliter

mmHg : millimeter of mercury

q–q : quantile-quantile

T2DM : type 2 diabetes mellitus

TRSC% : lower limb circumferences including tibial rough surface-calf 26%

Declarations

Ethics approval and consent to participate

The purpose of this study was explained orally and in writing, and only those who gave their 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 30015). This study was registered with the UMIN Clinical Trials Registry System (Trial ID UMIN000045445).

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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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.

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Tables
| Patient characteristics | Group | All  | Male  | Female | P value  |
|-------------------------|-------|------|-------|--------|----------|
|                         | n=114 | n=69 | n=45  |        |          |
| 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(/dl) | -     | 153.40±51.54 | 140.98±38.83 | 161.51±57.18 | 0.037    |
| Triglyceride(/dl)       | -     | 158.43±120.06 | 155.87±107.49 | 162.36±138.33 | 0.779    |
| HDL(mg/dl)              | -     | 57.37±14.47 | 59.98±15.97 | 55.73±13.30 | 0.137    |
| LDL(mg/dl)              | -     | 105.06±33.48 | 102.00±25.12 | 107.70±39.56 | 0.53     |
| T-Cho(mg/dl)            | -     | 198.86±36.12 | 210.94±28.50 | 194.02±38.00 | 0.114    |
| COPD (%)                | apply | 1 (0.9) | 1 (1.4) | 0 (0.0) | 1 |
|                         | Not applicable | 113 (99.1) | 68 (98.6) | 45 (100.0) |   |
| Hepatitis C (%)         | apply | 1 (0.9) | 1 (1.4) | 0 (0.0) | 1 |
|                         | Not applicable | 113 (99.1) | 68 (98.6) | 45 (100.0) |   |
| Hypertension (%)        | apply | 77 (67.5) | 44 (63.8) | 33 (73.3) | 0.313    |
|                         | Not applicable | 37 (32.5) | 25 (36.2) | 12 (26.7) |   |
| Epilepsy (%)            | apply | 1 (0.9) | 0 (0.0) | 1 (2.2) | 0.395    |
|                         | Not applicable | 113 (99.1) | 69 (100.0) | 44 (97.8) |   |
| Graves' disease (%)     | apply | 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 (%) | apply | 11 (9.6) | 6 (8.7) | 5 (11.1) | 0.75 |
|                         | Not applicable | 103 (90.4) | 63 (91.3) | 40 (88.9) |   |
| Condition                              | Apply | Male (%)     | Female (%)    | P value |
|---------------------------------------|-------|--------------|---------------|---------|
| cerebrovascular disease (%)           |       | 9 (7.9)      | 4 (5.8)       | 5 (11.1) | 0.314 |
|                                        |       | 105 (92.1)   | 65 (94.2)     | 40 (88.9) |
| Hashimoto's thyroiditis (%)            |       | 2 (1.8)      | 1 (1.4)       | 1 (2.2)  | 1     |
|                                        |       | 112 (98.2)   | 68 (98.6)     | 44 (97.8) |
| Hypothyroidism (%)                    |       | 4 (3.5)      | 4 (5.8)       | 0 (0.0)  | 0.152 |
|                                        |       | 110 (96.5)   | 65 (94.2)     | 45 (100.0) |
| hypercholesterolemia (%)              |       | 59 (51.8)    | 31 (44.9)     | 28 (62.2) | 0.086 |
|                                        |       | 55 (48.2)    | 38 (55.1)     | 17 (37.8) |
| dyslipidemia (%)                      |       | 17 (14.9)    | 11 (15.9)     | 6 (13.3)  | 0.792 |
|                                        |       | 97 (85.1)    | 58 (84.1)     | 39 (86.7) |
| hyperuricemia (%)                     |       | 12 (10.5)    | 10 (14.5)     | 2 (4.4)   | 0.121 |
|                                        |       | 102 (89.5)   | 59 (85.5)     | 43 (95.6) |
| osteoporosis (%)                      |       | 5 (4.4)      | 1 (1.4)       | 4 (8.9)   | 0.078 |
|                                        |       | 109 (95.6)   | 68 (98.6)     | 41 (91.1) |
| fatty liver (%)                       |       | 1 (0.9)      | 1 (1.4)       | 0 (0.0)   | 1     |
|                                        |       | 113 (99.1)   | 68 (98.6)     | 45 (100.0) |
| Chronic hepatitis (%)                 |       | 12 (10.5)    | 7 (10.1)      | 5 (11.1)  | 1     |
|                                        |       | 102 (89.5)   | 62 (89.9)     | 40 (88.9) |
| Chronic cardiac insufficiency (%)     |       | 1 (0.9)      | 0 (0.0)       | 1 (2.2)   | 0.395 |
|                                        |       | 113 (99.1)   | 69 (100.0)    | 44 (97.8) |
| Chronic renal insufficiency (%)       |       | 1 (0.9)      | 1 (1.4)       | 0 (0.0)   | 1     |
|                                        |       | 113 (99.1)   | 68 (98.6)     | 45 (100.0) |

| Neuropathy Group | All | Male | Female | P value |
|------------------|-----|------|--------|---------|
| n=114            | n=69| n=45 |        | Male versus female |

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| Abnormal ankle reflex(%) | apply | 59 (51.8) | 33 (47.8) | 26 (57.8) | 0.341 |
|--------------------------|-------|-----------|-----------|-----------|-------|
| Not applicable           |       | 55 (48.2) | 36 (52.2) | 19 (42.2) |       |
| Probable neuropathy(%)   | apply | 97 (85.1) | 55 (79.7) | 42 (93.3) | 0.060 |
| Not applicable           |       | 17 (14.9) | 14 (20.3) | 3 (6.7)   |       |
| Decreased vibration perception(%) | apply | 40 (35.1) | 23 (33.3) | 17 (37.8) | 0.690 |
| Not applicable           |       | 74 (64.9) | 46 (66.7) | 28 (62.2) |       |
| Number of neuropathy findings(%) | one  | 33 (28.9) | 18 (26.1) | 15 (33.3) | 0.425 |
| Number of neuropathy findings(%) | two  | 27 (23.7) | 15 (21.7) | 12 (26.7) |       |
| Number of neuropathy findings(%) | three | 43 (37.7) | 27 (39.1) | 16 (35.6) |       |
| Number of neuropathy findings(%) | four  | 11 (9.6)  | 9 (13.0)  | 2 (4.4)   |       |
| Sensory symptoms(%)      | apply | 45 (39.5) | 24 (34.8) | 21 (46.7) | 0.242 |
| Sensory symptoms(%)      | Not applicable | 69 (60.5) | 45 (65.2) | 24 (53.3) |       |

### Body composition and muscle strength

| Group                        | All | Male | Female | P value | Male versus female |
|------------------------------|-----|------|--------|---------|---------------------|
|                             | n=114 | n=69 | n=45   |         |                     |
| BMI(kg/m²)                   | -   | 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 |
| Femur 25% position circumference(mm) | -   | 40.24±5.06  | 40.34±4.3   | 40.08±6.1  | 0.788 |
| Femur 50% position circumference(mm) | -   | 46.65±5.57  | 47.34±5.02  | 45.59±6.24 | 0.102 |
| Calf 26% position circumference(mm) | -   | 36.01±3.86  | 36.75±3.56  | 34.87±4.07 | 0.010 |
| Calf 26% -Femur 25% (%)       | -   | 89.89±6.14  | 91.35±5.23  | 87.65±6.78 | 0.001 |
| Calf 26% -Femur 50% (%)       | -   | 77.43±4.68  | 77.8±3.95   | 76.87±5.62 | 0.300 |
| Arteriosclerosis Indicators | Group | All          | Male          | Female         | P value      |
|----------------------------|-------|--------------|---------------|----------------|--------------|
| n=114                      |       | n=69         | n=45          |                |              |
| 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 (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) \( \text{t-test, } \chi^2 \text{ test.} \)

HDL High density lipoprotein, LDL Low Density Lipoprotein, T-Cho 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
|                           | 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 (mg/dl)               | 0.080    | -0.11-0.264| 0.828   | 0.409    |
| LDL (mg/dl)               | 0.259    | -0.488-0.005| -1.967  | 0.054    |
| T-Cho (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/m²)               | -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   |
| Femur 25% position circumference (mm) | -0.381 | -0.528-0.212| -4.364  | <0.001   |
| Femur 50% position circumference (mm) | -0.483 | -0.613-0.328| -5.839  | <0.001   |
| Calf 26% position circumference (mm) | -0.516 | -0.639-0.367| -6.376  | <0.001   |
| Calf 26% -Femur 25% (%)    | -0.414   | -0.556-0.249| -4.811  | <0.001   |
| Calf 26% -Femur 50% (%)    | -0.212   | -0.381-0.029| -2.291  | 0.024    |
| Tibial rough surface-Femur 25% (%) | -0.101 | -0.28-0.084| -1.078  | 0.284    |
| Tibial rough surface-Femur 50% (%) | 0.034 | -0.151-0.217| 0.363   | 0.718    |
| TRSC (%)                  | -0.522   | -0.644-0.374| -6.470  | <0.001   |
|                          | Mean ± SD               | IQR   | p-value |
|--------------------------|-------------------------|-------|---------|
| 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-Cho 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
## Table 3. 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 (dl)           |   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
| Table 4. 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

Figures

[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 head of the most protruding part of the fibula and the most protruding part of the Lateral malleolus.
e: 26% the length of “d”
Dotted line : The part where the circumference was measured.

[Name of measurement point]
① : Femur 50% position circumference
② : Femur 25% position circumference
③ : Tibial rough surface position circumference
④ : Calf 26% position circumference (maximum calf circumference)

[Correction method (name= Correction formula ) ]
Calf 26% -Femur 25%(%) = ④/(① × 100
Calf 26% -Femur 50%(%) = ④/(② × 100
Tibial rough surface-Femur 50%(%) = ①/③ × 100
Tibial rough surface-Femur 25%(%) = ②/③ × 100
Tibial rough surface- calf 26%(%) = ④/③ × 100

Figure 1

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: part where the circumference was measured Name of measurement point: Femur 50% position circumference: Femur 25% position circumference: Tibial rough surface position circumference: Calf 26% position circumference: Tibial rough surface-calf 26% position circumference (maximum calf circumference) Correction method (name: correction formula) Calf 26% - Femur 25%(%) = / x 100. Femur 50%(%) = / x 100. Tibial rough surface femur 50%(%) = / x 100. Tibial rough surface-calf 26%(%) = / x 100.

Figure 2

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

\[
y = -36.658x + 5580.3 \\
r = -0.522 \\
\text{Pearson, } p<0.05
\]