Observational Study

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Subclinical atherosclerosis and sarcopenia
A prospective study

Ezgi Yilmaz, MD[a], Ethem Murat Arsava, MD[a], Mehmet Akif Topcuoglu, MD[a,*]

Abstract

The relationship between subclinical carotid artery atherosclerosis and sarcopenia has not been clarified in many respects. In this study, the possible relationship between composite clinical sarcopenia indices and various levels of subclinical atherosclerosis parameters was revisited. The Ishii score (Ishii-max and Ishii-average) was used to determine sarcopenia in 257 prospectively recruited healthy controls and patients with neurological diseases (age: 65 ± 10 years, 50% female). Carotid artery distensibility indices (stress, strain, modulus, stiffness, and distensibility), intima-media thickness (IMT-max and IMT-mean), and 10 Kate plaque burden score were obtained for ultrasonographic subclinical atherosclerosis evaluation, together with detailed clinical and anthropometric, quality of life, and nutritional assessments. Sarcopenic subjects (n = 75) were older, slimmer, and at higher risk of malnutrition (Malnutrition Universal Screening Tool score > 0) than nonsarcopenic subjects (n = 182). IMT-mean and IMT-max were significantly higher in sarcopenic cases (mean difference: 45 microns and 60 microns, respectively, $P < .05$). Carotid plaque burden score was significantly higher in sarcopenic patients (average score: 2.2 vs 0.8 in sarcopenic and nonsarcopenic ones, $P < .001$). There was no difference in terms of carotid artery distensibility parameters. In various regression models, the Ishii score was always determined as an independent predictor of IMT-max and IMT-mean in the models (standardized beta, from 0.132–0.168; partial-r, from 0.156–0.201; p, from 0.019–0.001). Structural indices of subclinical atherosclerosis (carotid IMT and plaque burden), but not functional ones (carotid artery modulus and distensibility), are significantly abnormal in sarcopenic subjects. If future research validates these findings, employing ultrasonographic atherosclerosis indices as surrogate markers in sarcopenia treatments could address a crucial unmet need.

Abbreviations: ADL = activities of daily living, CC = calf circumference, CCA = common carotid artery, DBP = diastolic blood pressure, DD = diastolic diameter, EAT-10 = The Eating Assessment Tool, HGS = hand grip strength, IMT = intima-media thickness, MUST = The Malnutrition Universal Screening Tool, PD = Parkinson disease, SARC-F = Acronym for "Sarcopenia screening test" "Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls" questionnaire, SarQoL = "Sarcopenia & Quality of Life" questionnaire, SBP = systolic blood pressure, SD = standard deviation, SD = systolic diameter, SPPB = short physical performance battery.

Keywords: atherosclerosis, carotid artery, malnutrition, muscle mass, ultrasonography, vascular

1. Introduction

Sarcopenia and cardiovascular events related to atherosclerosis are 2 common causes of functional decline in older adults and are likely interlinked.[1] This association may partly arise from vascular aging, which leads to impaired intramuscular microvascularization in sarcopenic muscles.[2] A growing number of studies have investigated the effects of vascular health on muscle function.[3–12] While some research directly examines the relationship between sarcopenia indices: such as muscle mass, strength, and functionality, and vascular health,[5,11] others focus on vascular status in connection to sarcopenia-related conditions such as frailty.[4,13]

Dysfunction and insufficiency in regional arteries supplying the extremity muscles, caused by steno-occlusive vascular lesions, have been shown to worsen sarcopenia.[14,15] However, the overall impact of systemic atherosclerosis on muscle health remains to be fully understood.[16] Notably, the direct relationship between asymptomatic (or preclinical/subclinical) atherosclerosis and sarcopenia/frailty has been examined in relatively few studies.[17] In these investigations, functional indices such as flow-mediated dilatation,[6] carotid-femoral or brachial-ankle

Written informed consent was obtained from all study participants.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of Hacettepe University and complied with the declaration of Helsinki.

[a] Department of Neurology, Hacettepe University, Faculty of Medicine Hospital, Ankara, Turkey.

** Correspondence: Mehmet Akif Topcuoglu, Department of Neurology, Hacettepe University, School of Medicine, Altindag, 06230 Ankara, Turkey (e-mail: matopcuoglu@yahoo.com).*

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pulse wave velocity[7,12,13] or cardio-ankle vascular index,[10,11,18] as well as structural markers such as coronary artery calcification,[19] carotid intima-median thickness (IMT),[5,7,11,20] and asymptomatic atheroma plaque burden[21] have been studied. In most, but not all,[4,7,12,22,23] of these few studies, the negative impact of subclinical atherosclerosis on muscle health has been partially emphasized.[10,11,13,19–21,24,25] Our research has focused on the multifaceted link between sarcopenia and ultrasonographic markers reflecting both structural and functional aspects of subclinical atherosclerosis.

2. Methods

2.1. Study population

A total of 257 people (age: 65 ± 10 years, 50% female) were enrolled in the study. The study population included 152 apparently healthy control subjects without any complaints and 105 independently mobile patients with neurological disease or symptoms. The latter were consecutive patients admitted to the neurology outpatient clinic of our hospital between October 2018 and March 2020. The final neurological disease diagnoses were as follows: dementia spectrum in 75 patients, Parkinson disease (PD) in 18, multiple sclerosis in 10, PD with dementia in 1, and minor stroke in 1. The control group consisted of volunteer relatives of these patients. Subjects with impaired gait and motor deficits were excluded. The clinical scales used for neurological diseases were the Expanded Disability Status Scale[26] for multiple sclerosis, the modified Hoehn&Yahr scale[27] for PD, and the Mini Mental State Examination [28] for dementia. The average scores for Expanded Disability Status Scale, the modified Hoehn&Yahr scale, and the Mini Mental State Examination were 2.5 ± 2, 2 ± 1.1, and 26 ± 5.6, respectively. In addition, individuals with coronary artery disease history or those taking statins were excluded from the study. Written consent was obtained from all persons and, if necessary, from their relatives for all procedures. Study protocols were approved by the ethics committee of Hacettepe University.

2.2. Demographic, clinical, and anthropometric data

Age, gender, educational status, atherosclerosis risk factors, all diseases, and medicines used, smoking and alcohol use history were recorded. Height, weight, body mass index, upper middle arm circumference, calf circumference (CC), thigh circumference, waist circumference, and hip circumference were measured by a trained study neurologist (EY).

2.3. Clinical tests for sarcopenia, physical activity, and frailty

Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls (SARC-F) and Sarcopenia & Quality of Life" (SarQoL) questionnaires[29,30] were performed in all, along with short physical performance battery (SPPB, ≤8 abnormal).[31] Frequency of falls, Morse fall scale,[32] Barthel index for activities of daily living (ADL),[33] Lawton and Brody Instrumental ADL,[34] fatigue severity scale,[35] fall efficacy scale,[36] and Beck depression inventory[37] were determined for all subjects. In addition, the Malnutrition Universal Screening Tool (MUST),[38] functional oral intake scale,[39] and the Eating Assessment Tool (EAT-10)[40] were obtained for all subjects.

2.4. Hand grip strength test

Hand grip strength (HGS) test was performed with a Takei (T.K.K.5401 GRIP D) handheld dynamometer using the standardized method recommended by the European Working Group on Sarcopenia in Older People.[41] The subjects were asked to grasp and squeeze the dynamometer in a sitting position with their forearms on the chair armrest and their thumbs facing up. Starting from the right side, resting for 30 seconds in between, 3 measurements were recorded alternately from each hand. Along with mean of all attempts, the highest measurement values were considered in the analysis ("HGSmean" and "HGSmax," respectively). According to the published values for the Turkish population, cutoff values of HGS < 32 kg for men and < 22 kg for women were used.[42]

2.5. Ishii score

Ishii score was calculated using original formula: Ishii score = 0.80 × (age - 64) - 5.09 (HGS - 34) - 3.28 (CC - 42) for women and Ishii score = 0.62 × (age - 64) - 3.09 × (HGS - 50) - 4.64 (CC - 42) for men. Ishii score was calculated separately for HGS mean and HGSmax (Ishii-average and Ishii-max, respectively). Women with Ischii score higher than 120 and men with Ishii score higher than 105 were labeled as high probability of sarcopenia.[43,44] Measurements were performed by a trained study neurologist (EY).

2.6. Ultrasound studies

2.6.1. Carotid artery distensibility. All recordings were performed with the 7 to 12 MHz linear transducer of the Logiq® P6 ultrasound system (GE, Milwaukee, WI), with the patient lying supine, with the head in a neutral and low semi-Fowler position. Studies were performed by a neurosonologist [MAT] with over 20 years of experience who was completely blind to the diagnosis and other relevant information of subjects, using standard insonation techniques of the common carotid artery (CCA), internal carotid artery, and external carotid artery on both sides. The M-mode scan line was placed approximately in the middle third of the CCA where the largest transverse vessel diameter was visually identified. In general, recordings were taken from the internal jugular vein window with the lateral approach without applying any pressure on the CCA. At least 10 cardiac cycles were recorded, but the maximum 3 were averaged. In other words, the maximum and minimum diameters in the same cardiac cycle were measured (Fig. 1A). Brachial systolic and diastolic blood pressure (SBP and DBP) were measured noninvasively (Omron® M3). Systolic and diastolic diameter [SD and DD] were measured in both CCAs and the average of 3 measurements was taken. After measuring each parameter on the right and left in this way, a single value was obtained for each patient by averaging. Measurements were made offline. From these data, distensibility metrics were calculated: "Strain"= (SD - DD)/DD; "Stiffness" [β] = ln(SBP/DBP)/strain; "Distensibility" = 1/β, and "Young elastic modulus" E = 133.3 × (SBP - DBP)/strain.[45]

2.6.2. IMT. The IMT measurement technique fully complies with the latest Mannheim consensus criteria.[46] Briefly, recordings were performed in 2-D ultrasound (B mode) from the posterior wall of the CCA on each side, in a segment at least 1 cm in length in the mid-proximal part of CCA, and at a distance of 1-cm closest to its bifurcation. Linear transducer 7 to 12 MHz was used (Logiq® P6, GE, Milwaukee, WI). Measurements were performed offline with the GE Auto-IMT® program, which performs automatic edge detection. For the "Gain" setting, the near and far CCA wall is ensured to be of the same brightness, and the gain is reduced if the automatic line overflows within the lumen in edge detection. The measured parameters are "maximum IMT (IMT-max)," "average IMT (IMT-mean)," "minimum IMT (IMT-min)," and "IMT standard deviation (IMT-SD)." In addition, the measuring point [must

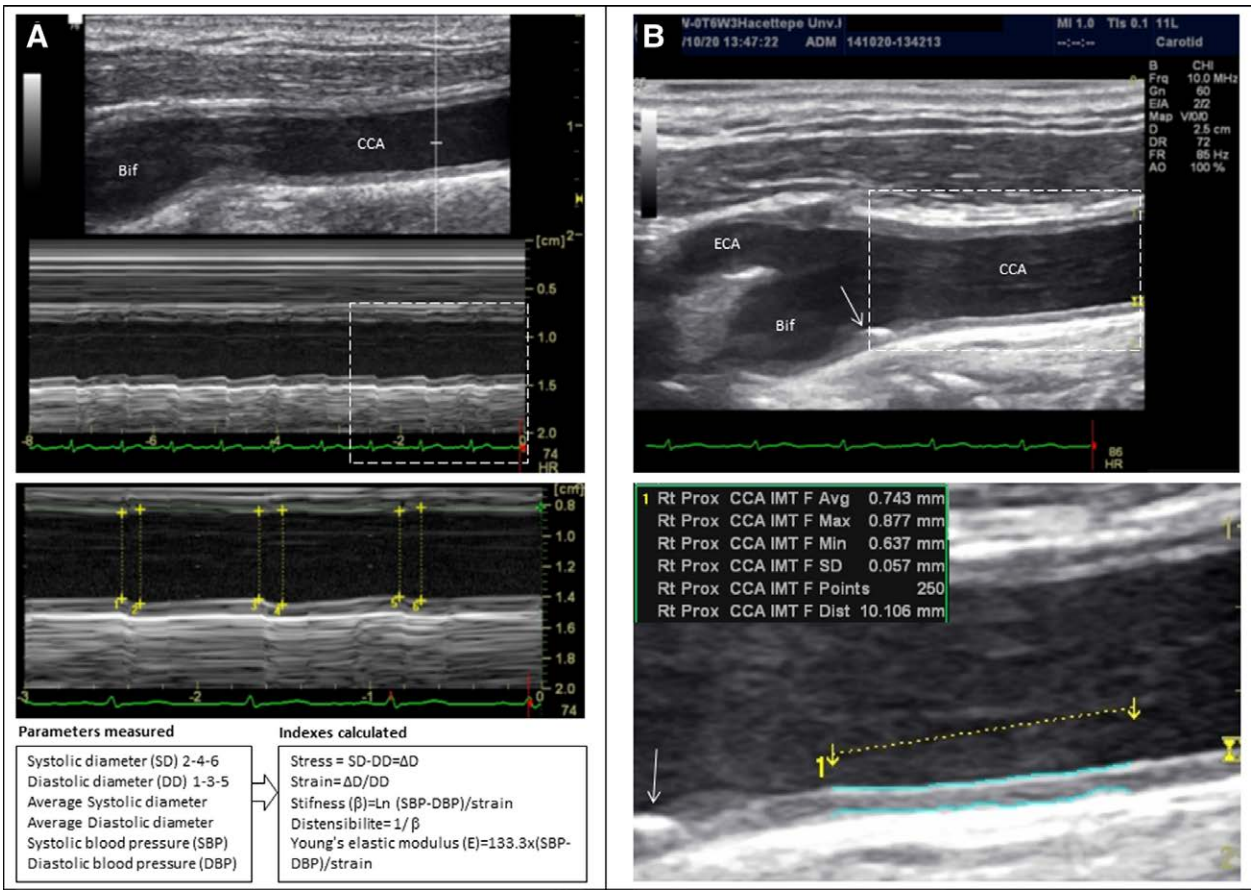

Figure 1. Carotid artery distensibility and carotid intima-media thickness measurement techniques. Panel A (left): the top section shows the placement of the scan line for measuring carotid artery distensibility. The middle section presents an M-mode recording of the common carotid artery across 10 cardiac cycles, accompanied by ECG monitoring. Below, the dashed-line box in the middle section is magnified 3 times, showcasing the documentation of diastolic and systolic diameter measurements. At the bottom, the measured parameters are explained. Panel B (right): The upper section shows the part of the common carotid artery where IMT was measured in B-mode images. The dashed box is enlarged 3 times and given below. IMT-max, IMT-min, IMT-average, and IMT-SD values were measured from 250 points of 10 mm length from the posterior wall. (See text for abbreviations and parameters used in ultrasound measurement. White arrow indicates small-sized plaque formation. Bif = carotid bifurcation, CCA = common carotid artery, ECA = external carotid artery), IMT = intima-media thickness, max = maximum, min = minimum, SD = standard deviation.

be at least 150] and the length [must be at least 1-cm] were noted (Fig. 1B). Measurements were made from areas devoid of atherosclerotic plaque. Care was taken to ensure that there was a 5-mm gap between the plaque and the area where IMT measurement was performed. Insonation was performed by passing through the internal jugular window, and approaching laterally and vertically, to ensure visualization of the maximum diameter of the CCA longitudinally, thereafter which the screen was frozen and recorded. Thus, it was ensured that no extra-central tangential sections were taken.

2.6.3. Plaque burden score. The "Carotid plaque burden score" that ten Kate et al created[47] was used. Briefly, "0" point is given if there is no plaque, "1" point as the maximum plaque thickness (vertical luminal protrusion) is between 1 and 2.5 mm, "2" point for 2.51 to 3.5 mm, and "3" point for > 3.5 mm. Scoring was performed for a rostral 15-mm length at the common carotid artery and carotid bifurcation, and for a caudal 30-mm length at the internal carotid and external carotid arteries. With this scoring system, a maximum of 12 points can be obtained on 1 side and 24 points bilaterally (Fig. 2). If the modified ten Kate score is not 0, it means that there is an atherosclerotic plaque, and in this case the stenosis grading was performed as per Neurosonology Research Group of the World Federation of Neurology criteria set.[48]

2.7. Statistics

All data were presented as mean ± standard deviation, median (minimum–maximum or ± interquartile range), or percent as appropriate. Distribution normality was examined by Shapiro–Wilk and Kolmogorov–Smirnov tests. Student *t*, Mann–Whitney *u*, or analysis of variance (ANOVA) tests were used for numerical values, and chi-square or Fisher exact tests were used for categorical variables. Pearson and Kendall tau-b methods were used for correlation analysis, as appropriate. Exploratory multiple regression models were created for both Ishii score (Ishii-max and Ishii-average as "dependent") with inclusion of independent variables with $P < .1$ in univariate analyses. Analysis results were reported with standardized beta (sβ), partial (adjusted) correlation coefficient (r_p) and P value along with adjusted R^2 (aR^2), variance inflation factor and Durbin–Watson values as model characteristics. A P value <.05 was accepted for statistical significance. SPSS® version 22.0 package statistics program (Armonk, NY: IBM Corp.) was used for all analyses.

3. Results

3.1. Population

According to Ishii score tables, there were 75 sarcopenic and 182 nonsarcopenic subjects in our study cohort. Age was higher in the sarcopenia group (73 ± 8 vs 62 ± 10, $P < .001$), and no

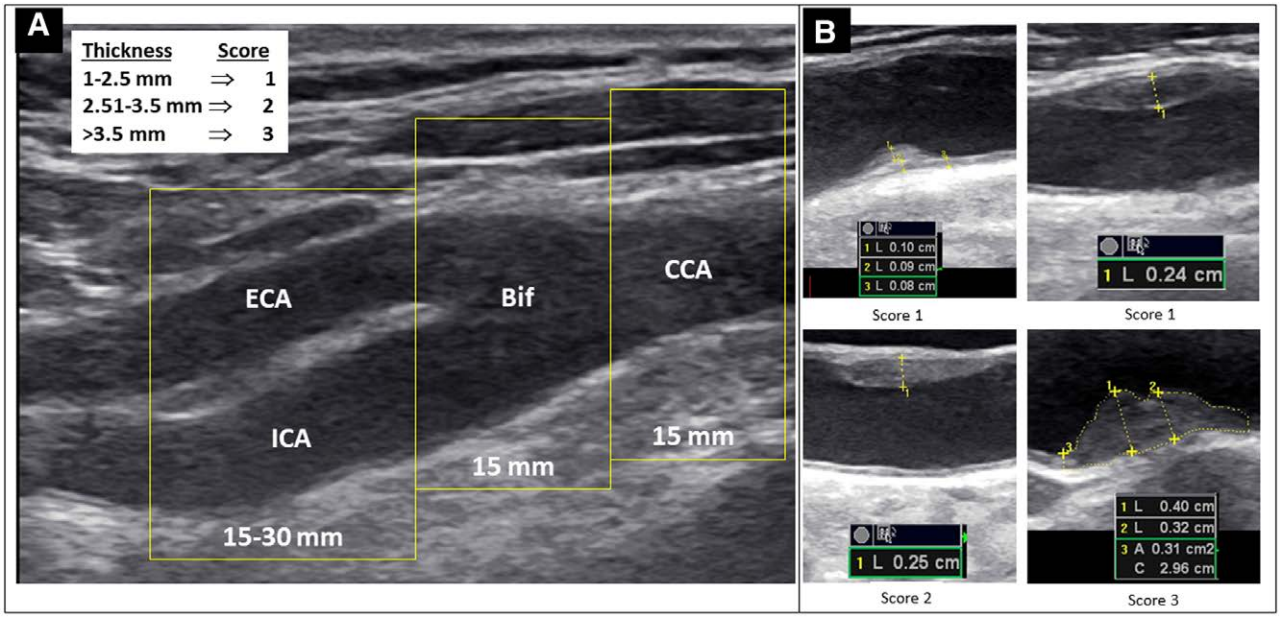

Figure 2. Plaque burden scoring. Panel A (left) illustrates the vascular regions where the ten Kate carotid plaque burden score was assessed. Measurements were taken over a rostral 15-mm segment of the common carotid artery and the carotid bifurcation, as well as a caudal 30-mm segment of the internal and external carotid arteries. Panel B (right) presents examples of atheroma plaques assigned scores of 1, 2, and 3. Bif = bifurcation, CCA = common carotid artery, ECA = external carotid artery, ICA = internal carotid artery.

difference was found in terms of gender. Although an increasing trend was noted in sarcopenic cases, there was no significant difference in the frequency of hypertension, dyslipidemia, and diabetes (Table 1A).

People in the sarcopenia group were shorter and leaner. Body mass index, waist, and hip circumference were lower (Table 1B).

SPPB score was 1.7 points lower in sarcopenic subjects, and the rate of the SPPB score below 9 was significantly higher (approximately 3.7 times) in this group. As anticipated, the sarcopenic group had higher SARC-F scores and abnormal (>4) SARC-F score frequencies. Additionally, the sarcopenic cases had significantly worse quality of life measures such SarQoL, the Barthel index, and the Lawton–Brody Instrumental ADL Scale. The sarcopenic group had higher rates of clinical outcomes related to sarcopenia, including severe fatigue rate (FSS > 6) and high fall risk (Table 1C).

The MUST score 0 was significantly lower in the sarcopenic subjects (70.7% vs 92.3%, $P < .001$). This indicates that the risk of malnutrition is significantly increased in these cases. In addition, the median MUST score was higher in the sarcopenic cases. While there was no difference between the groups in terms of EAT-10 and functional oral intake scale scores, the rate of EAT-10 >3 was twice as high in sarcopenic participants ($P = .036$) (Table 1D).

3.2. Subclinical atherosclerosis indices

IMT was significantly higher in the sarcopenic group. The approximate mean differences for the IMT-mean were 45 microns; 60 microns for IMT-max, and 41 microns for IMT-min. Quality of measurement was not different between groups, as evidenced by similar IMT-SD and number or length points. Carotid plaque burden score was significantly higher in sarcopenic subjects. There was no difference between the groups in any of the carotid artery distensibility parameters (Table 2).

3.3. Sarcopenia and subclinical atherosclerosis

In the model created by including Ishii-max as "dependent" and IMT-max with "independent variables" ($aR^2 = 0.381$) IMT-max was found as an independent determinant of Ishii-max ($s\beta = 0.180$ and $r_p = 0.212$). In this model (power of model > 0.95, retrospectively), there was a negative correlation between height and weight and the Ishii-max score, while the MUST score and the Ishii-max score showed a moderate but significant positive correlation ($P = .010$). Plaque score and atherosclerosis risk factors were not significant determiners in the model (Table 3). When we repeated these calculations for pairs "Ishii-max and IMT-mean," "Ishii-average and IMT-max," and "Ishii-average and IMT-mean," we confirmed the similar relationship (sβ: between 0.132–0.168, r_p: between 0.156–0.201, $P < .05$ for all 3). The models show moderate explanatory capacity (at the one-third level), acceptable multicollinearity (variance inflation factor: between 1.150–1.172), and autocorrelation (Durbin–Watson: between 1.672–1.735) (Table 4). Figure 3 presents scatter plots illustrating the relationship between Ishii-max or Ishii-mean scores and IMT-max or IMT-min values, with data points labeled by gender. The relationship between sarcopenia and subclinical atherosclerosis seems comparable across male and female subgroups. Key anthropometric parameters such as thigh circumference ($r = -0.145$, $P = .028$), calf circumference ($r = -0.238$, $P < .001$), and mid-arm circumference ($r = -0.296$, $P < .001$) demonstrated weak but statistically significant inverse correlations with the plaque burden score. However, MUST did not show a significant correlation with the plaque burden score ($R = 0.065$, $P = .325$). Information regarding the relationships between other anthropometric measurements and additional subclinical atherosclerosis indices is not included here.

4. Discussion

We herein document a positive correlation between sarcopenia and subclinical atherosclerosis as demonstrated by IMT increase. The IMT sarcopenia link is independent of plaque burden and vascular risk factors. In addition to height and weight, the only independent factor contributing to this association was the risk of malnutrition (higher MUST score). A nonindependent positive correlation was also noted between asymptomatic carotid plaque burden and sarcopenia.

Table 1

Demographics and characteristics of sarcopenia.

	Sarcopenic	Nonsarcopenic	
N	**75**	**182**	
(A) Demographic			
Age	72.7 ± 8.3	61.9 ± 10.2	<0.001
Female gender	58.7%	63.2%	0.498
Hypertension	46.7%	37.9%	0.194
Dyslipidemia	18.7%	13.1%	0.161
Diabetes mellitus	26.7%	18.1%	0.124
(B) Physical			
Height (cm)	156.2 ± 8.2	160.9 ± 9.4	<0.001
Body weight (kg)	64.8 ± 11	76.3 ± 13.8	<0.001
Body mass index (kg/m^2)	26.6 ± 4.3	29.6 ± 5.4	<0.001
Waist circumference (cm)	92.2 ± 11.9	97.9 ± 13.1	0.001
Hip circumference (cm)	101.4 ± 8.1	106.4 ± 10.1	<0.001
(C) Function/sarcopenia			
Short physical performance battery	9.2 ± 2.8	10.9 ± 1.6	<0. 001
SPPB < 9	30.7%	8.2%	<0.001
SARC-F	[2 ± 4] 2.4 ± 2.4	[0 ± 2] 1.0 ± 1.5	<0.001
SARC-F > 4	30.7%	8.2%	<0.001
SARQoL	66.9 ± 17.1	79.1 ± 16.6	<0.001
Fatigue severity scale	4.8 ± 7.6	4.9 ± 11.5	0.943
FSS > 6	46.5%	27.6%	0.004
Morse fall scale	25.3 ± 18.9	13.3 ± 14.4	<0.001
Low risk	63.9%	87%	<0.001
Medium risk	26.4%	10.7%	
High risk	9.7%	2.3%	
Beck depression scale	10.9 ± 9.0	9.9 ± 8.5	0.457
Barthel index for ADL	96 ± 7	98 ± 5	0.002
Barthel index < 100	38.6%	19.9%	0.002
Lawton–Brody Instrumental ADL Scale	6.2 ± 2.2	7.5 ± 1.3	<0.001
HGS mean	16.6 ± 5.3	24.7 ± 8.2	<0.001
HGS max	19.7 ± 6.1	28.1 ± 8.9	<0.001
(D) Nutrition			
MUST	0 ± 1 (0.4 ± 0.7)*	0 ± 0 (0.1 ± 0.4)*	<0.001
0	70.7%	92.3%	<0.001
1	17.3%	4.4%	
2	10.7%	3.3%	
3	1.3%	0.0%	
MUST > 0	29.3%	7.7%	<0.001
EAT-10	1.9 ± 5.4	0.9 ± 2.5	0.050
EAT-10 > 3	21.1%	10.9%	0.036
FOIS < 7	2.7%	1.6%	0.238

ADL = activities of daily living, EAT-10 = Eating Assessment Tool, FOIS = functional oral intake scale, FSS = fatigue severity scale, HGS = hand grip strength, IQR = interquartile range, MUST = Malnutrition Universal Screening Tool, SARC-F = "Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls" score, SarQoL = Sarcopenia & Quality of Life Score, SPPB = short physical performance battery.

*Median ± IQR (mean ± SD).

Table 2

Subclinical atherosclerosis indices in sarcopenic patients without history of coronary heart disease or statin use.

	Sarcopenic	Nonsarcopenic	
N	**75**	**182**	
Plaque burden score	[1 ± 3] 2.230 ± 3.195	[0 ± 1] 0.808 ± 1.472	<0.001
IMT-mean	0.715 ± 0.134	0.670 ± 0.132	0.018
IMT-max	0.913 ± 0.177	0.853 ± 0.174	0.017
IMT-min	0.526 ± 0.126	0.485 ± 0.119	0.020
IMT-SD	0.087 ± 0.028	0.09 ± 0.059	0.746
IMT-point	274.5 ± 34.9	278.4 ± 40.3	0.478
Stress	0.084 ± 0.026	0.082 ± 0.024	0.518
Strain	0.137 ± 0.047	0.131 ± 0.038	0.268
Modulus	58279.0 ± 30930.2	53791.2 ± 24352.1	0.231
Stiffness	4.204 ± 2.293	3.812 ± 1.649	0.137
Distensibility	0.301 ± 0.126	0.327 ± 0.326	0.530

Numbers are mean ± standard deviation. Number in square brackets is median ± interquantile range.

IMT = intima-media thickness, max = maximum, min = minimum, SD = standard deviation.

Table 3

Regression analysis.

	sβ	r_p	*P*
IMT-max	0.181	0.212	.001
Distensibility	-0.036	0.046	.494
Total plaque score	0.076	0.093	.166
MUST	0.143	0.172	.010
Height (cm)	-0.201	-0.221	.001
Weight (kg)	-0.405	-0.396	<.001
Hypertension	0.056	0.067	.166
Diabetes mellitus	0.076	0.095	.158
Dyslipidemia	0.047	0.059	.381

IMT = intima-media thickness, max = maximum, MUST = Malnutrition Universal Screening Tool, r_p = partial (adjusted) correlation coefficient, sβ = standardized beta.

Table 4

Statistical characteristics of regression models.

Dependent	Ishii-max	Ishii-max	Ishii-mean	Ishii-mean
Independent	IMT-max	IMT-average	IMT-max	IMT-average
aR^2	0.381	0.369	0.393	0.382
Durbin–Watson	1.743	1.735	1.679	1.672
VIF	1.150	1.172	1.150	1.172
sβ	0.181	0.142	0.168	0.132
r_p	0.212	0.166	0.201	0.156
P	.001	.013	.002	.019

aR^2 = adjusted coefficient of determination, IMT = intima-media thickness, max = maximum, r_p = partial (adjusted) correlation coefficient, sβ = standardized beta, VIF = variance inflation factor.

A growing body of research has been examining the impact of vascular factors on muscle health, with a focus on sarcopenia-related aspects such as muscle mass, strength, and functionality. These studies explore not only sarcopenia indices, but also associated conditions like frailty to better understand their interconnections.[10] In these studies, the most commonly used method for sarcopenia is bioelectrical impedance-produced skeletal muscle mass index, while HGS is the most preferred muscle strength quantification method.[18] In this respect, the Ishii index was used for the first time in our study. Ishii index supports reliable models with fewer patients as it includes HGS, calf anthropometry, age, and sex. From a vascular point of view, macrovascular and microvascular beds were studied. The most frequently preferred methods for vascular evaluation are arterial stiffness tests such as cardio-ankle vascular index[10,11,18] and brachial-ankle/carotid-femoral pulse wave velocity measurement,[3,4,7,12,13] functional tests such as flow-mediated dilatation,[6,49] and structural indices such as coronary artery calcium score,[19,49] IMT,[5,7,11,20,24] and asymptomatic atherosclerotic plaque presence or burden.[21,24] In this context, for the first time, we used carotid artery distensibility in combination with IMT and asymptomatic plaque burden. Microvascular assessment such as capillary density, or microvascular flow via contrasted ultrasound has also been, albeit rarely, used in these studies.[17] Positive correlations between sarcopenia indices and parameters of atherosclerosis, subclinical atherosclerosis, or preclinical atherosclerosis have been documented in most, albeit not in all,[4,7,12,22,23] of the studies.[10,11,13,19–21,24,25,50] Our study supports this link in several dimensions. In many studies, it has been found that muscle strength loss increases as atherosclerosis

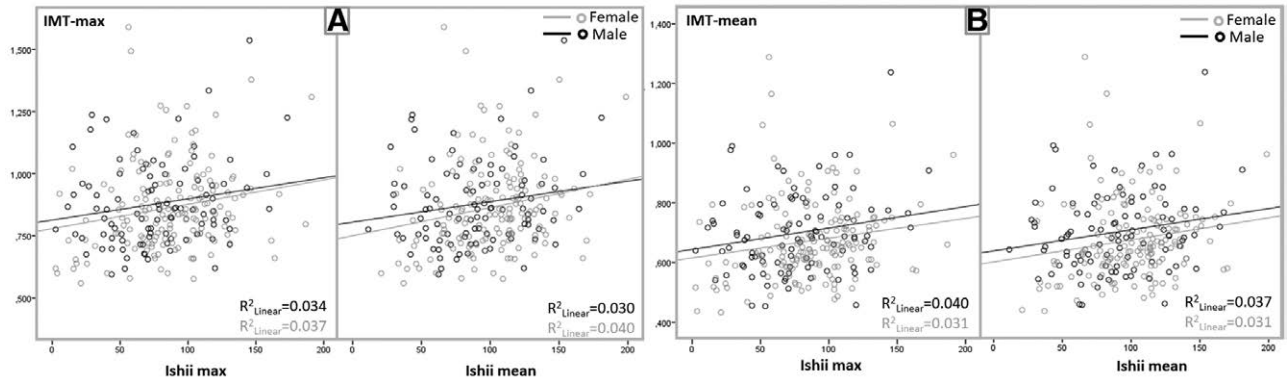

Figure 3. Scatter plot graphs. Panel A displays scatter plots of IMT-max against Ishii-max (left) and Ishii-mean (right) scores. Panel B illustrates scatter plots of IMT-mean against Ishii-max (left) and Ishii-mean (right) scores. Data points for females are represented in gray, while those for males are in black. IMT = intima-media thickness, max = maximum.

worsens.[17,18] Our findings illustrated that increased carotid artery IMT and atherosclerotic plaque burden had a significant negative effect on muscle health. In contrast, decreased carotid artery distensibility did not exert any notable negative influence on muscle health. One reason for this observation could be speculated to be that preclinical atherosclerosis does not lead to sarcopenia in its earlier stages characterized by vascular dysfunction alone.[4,7] However, atherosclerosis progresses over time and IMT thickening and plaque formation develop. At this more advanced stage of atherosclerosis, characterized by the development of structural changes, muscle health is adversely affected probably due to insufficiency of skeletal muscle microcirculation.[51] The positive association found in our study between low skeletal muscle mass and atherosclerosis is independent of age and gender, as in most previous studies,[16,52] although some studies have found a more pronounced association in men,[11,53,54] while others have found this association only in women.[55,56]

There are various hypotheses regarding the mechanisms underlying the association of sarcopenia and (sub)clinical atherosclerosis. Firstly, sarcopenia is seen as a result of significant or advanced atherosclerosis resulting in clinical heart diseases.[1,57] In addition, peripheral arterial diseases can directly lead to muscle ischemia and muscle wasting.[15,58] However, the coexistence of sarcopenia and atherosclerosis from the early stages does not seem to be explained by the macrovascular disease caused by atherosclerosis. But, it is logical that intramuscular microvascular disease may cause or facilitate sarcopenia from the early stages. It has been shown that muscle capillarization (capillary-to-fiber ratio) decreases in sarcopenia and that it reduces exercise capacity by limiting diffusion of substrates, oxygen, hormones, and nutrients to muscle tissues.[59] This is a manifestation of atherosclerosis similar to capillary rarefaction frequently seen in hypertensive patients.[60] The increase in cerebral white matter disease and cognitive impairment with sarcopenia may also be partially related to this mechanism.[61] The first mechanism that comes to mind in this context is that atherosclerosis and sarcopenia share many risk factors and underlying conditions such as age, sedentary lifestyle, oxidative stress, insulin resistance, and low testosterone levels.[62] Also, the effect will be magnified as atherosclerosis and sarcopenia will mutually increase the negative effects of each other. Sarcopenia-related physical inactivity and reduced exercise performance can promote the development of atherosclerosis. Atherosclerosis impairs muscle microvascularization, initially leading to compromised muscle strength and performance during exercise, and eventually to limitations in daily activities and increased frailty. Recent literature supports this mechanistic link by showing that physical activity and exercise improve muscle and vascular health by preventing or attenuating both sarcopenia and atherosclerosis.[63] Another factor in the link is likely to be chronic systemic inflammation.[64] Recent evidence suggests that gut microbiota may influence cardiovascular health and systemic inflammation,[65] potentially contributing to the observed association between subclinical atherosclerosis and sarcopenia via malnutrition and inflammatory pathways.

Although not supported in every study,[11,23,54] a negative correlation has been shown between IMT and HGS,[11] between IMT and skeletal muscle mass,[24,66] and between IMT and physical performance.[5,67] However, modern IMT measurement techniques were not used in almost any of these studies.[7,11,22,67] We contributed by determining that IMT values measured by the automatic edge identification method were significantly higher in sarcopenic cases and were an independent marker for sarcopenia. Another contribution of our study is to examine the problem in the atherosclerosis sarcopenia puzzle with new variables such as carotid distensibility and Ishii chart score.

Our study, which represents the clearest evidence to date linking sarcopenia with subclinical atherosclerosis, is not exempt from certain limitations. Approximately 40% of the participants had a diagnosed neurological disease. Although these individuals demonstrated normal motor function and ambulatory ability, it cannot be fully ruled out that their condition may have impacted the observed association between sarcopenia and subclinical atherosclerosis. Additionally, our regression models exhibit moderate explanatory capability. Incorporating key variables, such as inflammatory markers or physical activity levels, data that was not gathered in this study, could have significantly enhanced the models' overall strength.

In summary, our study has enhanced the current understanding of the relationship between subclinical atherosclerosis and sarcopenia. Looking ahead, 2 key questions emerge for future research. First, can treating subclinical atherosclerosis with risk factor control lead to improvements in sarcopenia outcomes? Second, is it feasible to use subclinical atherosclerosis markers to track the effectiveness of sarcopenia treatments? While our findings provide some initial support for these hypotheses, additional focused research is both necessary and urgent.

Author contributions

Conceptualization: Ezgi Yilmaz, Ethem Murat Arsava, Mehmet Akif Topcuoglu.
Data curation: Ezgi Yilmaz, Ethem Murat Arsava, Mehmet Akif Topcuoglu.
Formal analysis: Ezgi Yilmaz, Ethem Murat Arsava, Mehmet Akif Topcuoglu.

Funding acquisition: Mehmet Akif Topcuoglu.
Investigation: Ezgi Yilmaz, Mehmet Akif Topcuoglu.
Methodology: Ezgi Yilmaz, Ethem Murat Arsava, Mehmet Akif Topcuoglu.
Project administration: Mehmet Akif Topcuoglu.
Resources: Mehmet Akif Topcuoglu.
Software: Mehmet Akif Topcuoglu.
Supervision: Mehmet Akif Topcuoglu.
Writing – original draft: Mehmet Akif Topcuoglu.
Writing – review & editing: Ezgi Yilmaz, Ethem Murat Arsava, Mehmet Akif Topcuoglu.

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