SARcopenia Assessment in Hypertension

The SARAH Study

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Objectives: The aims of the study were to investigate the relationship between sarcopenia and renin-angiotensin system–related disorders and to explore the effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on muscle mass/function and physical performance.
Design: This multicenter, cross-sectional study was performed using ISarcoPRM algorithm for the diagnosis of sarcopenia.
Results: Of the 2613 participants (mean age = 61.0 ± 9.5 yrs), 1775 (67.9%) were hypertensive. All sarcopenia-related parameters (except chair stand test in males) were worse in hypertensive group than in normotensive group (all $P < 0.05$). When clinical/potential confounders were adjusted, hypertension was found to be an independent predictor of sarcopenia in males (odds ratio = 2.403 [95% confidence interval = 1.514–3.813]) and females (odds ratio = 1.906 [95% confidence interval = 1.328–2.734], both $P < 0.001$). After adjusting for confounding factors, we found that all sarcopenia-related parameters (except grip strength and chair stand test in males) were independently/negatively related to hypertension (all $P < 0.05$). In females, angiotensin-converting enzyme inhibitors users had higher grip strength and chair stand test performance values but had lower anterior thigh muscle thickness and gait speed values, as compared with those using angiotensin II receptor blockers (all $P < 0.05$).
Conclusions: Hypertension was associated with increased risk of sarcopenia at least 2 times. Among antihypertensives, while angiotensin-converting enzyme inhibitors had higher muscle function values, angiotensin II receptor blockers had higher muscle mass and physical performance values only in females.

What Is Known

- Hypertension has negative effects on muscle mass, muscle function and physical performance.

What Is New

- Hypertension was found to increase the risk of sarcopenia at least two-fold in both sexes.
- Because the highest frequency of sarcopenia (35.4%) was observed in male patients using angiotensin II receptor blockers and because angiotensin-converting enzyme inhibitors (ACEIs) use was positively related to muscle function, ACEIs may be preferred in people at risk for sarcopenia.

Key Words: Grip Strength, Angiotensin-Converting Enzyme Inhibitors, Muscle Function, Quadriceps, Ultrasound

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Age-related loss of skeletal muscle mass and function, defined as sarcopenia, is significantly related to adverse health outcomes, for example, increased risk of falls and fractures, physical frailty, mobility limitation, and even premature mortality.[1]

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Besides, aging, smoking, physical inactivity, malnutrition, and chronic comorbid diseases such as hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), hyperlipidemia, and obesity also have deteriorative effects on muscle mass and function.[2] Prevention of sarcopenia-related morbidity and mortality, among aging people in particular, depends on early detection and treatment, more importantly on unraveling the relationships between muscle loss, decline in muscle function and physical performance, and the aforementioned potential predictors.[3] To our best knowledge, there is no study investigating the relationships of renin-angiotensin system (RAS)-related disorders with the diagnostic criteria for sarcopenia.

Hypertension, a RAS-related disorder, has been most widely investigated with regard to its effect on muscle mass and function, and overactivation of RAS has been revealed to contribute to sarcopenia via affecting skeletal muscle metabolism.[4–6] Furthermore, RAS inhibitor antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACEIs), were speculated to be protective against loss of muscle mass and function among hyperpertensives.[7–9] However, results are conflicting and inconclusive.

On the other hand, although sarcopenia was recognized as a disease in the *International Classification of Diseases, Tenth Revision,* code in 2016,[10] it has no consensus on clinical definition or diagnostic criteria. Accordingly, the causes and prevalence of sarcopenia as well as its management and prognosis are being clouded. Most of the working groups for sarcopenia suggest to use appendicular skeletal muscle mass for the confirmation of muscle loss.[1,11] However, early/accurate detection of muscle loss can be performed through measurements on the anterior thigh region, known to be rich in fast-twitch (type II) muscle fibers and be affected early by aging and age-related chronic disorders.[1,12] Furthermore, studies have shown that anterior thigh (rather than total/appendicular skeletal muscle mass) muscle mass measurements are better correlated with muscle power/strength and performance tests.[13,14] In this regard, a recent diagnostic algorithm for sarcopenia emphasized the loss of anterior thigh muscle mass and function and drew attention to the risk among patients with chronic comorbid diseases, particularly RAS-related disorders.[1] To diagnose sarcopenia, algorithms recommend measurements of the anterior thigh muscle thickness (for muscle mass), grip strength and chair stand test (CST, for muscle function), and gait speed (for physical performance).

To this end, a multicenter, cross-sectional study was conducted to evaluate the relationship between the diagnostic criteria for sarcopenia and RAS-related disorder (especially HT) among middle-aged and older adults. Potential effects of RAS inhibitors on muscle mass/function and physical performance were further studied in the subgroup of hypertensive patients.

METHODS

Between January 2019 and December 2021, a total of 2613 individuals (aged 45–93 yrs) were recruited from multiple centers, that is, outpatient clinics of physical and rehabilitation medicine and internal medicine (Table 1). Subjects with Parkinson disease, previous stroke, cerebellar diseases, multiple sclerosis, major depression, neuromuscular diseases, history of major orthopedic surgery, severe hip/knee osteoarthritis, rheumatologic diseases, malignancies, advanced heart/liver/renal failure, visual impairment, and vestibular diseases and those using any assistive device for walking were excluded from the study. All eligibles

TABLE 1. Distribution of demographic/clinical characteristics and confounding factors by sex and hypertension status ($N = 2613$)

	Male			Female		
Characteristic	**Normotensive**	**Hypertensive**	***P***	**Normotensive**	**Hypertensive**	***P***
n	269	544		562	1238	
Age, yr	62.6 ± 9.7	62.5 ± 10.3	0.976	58.6 ± 9.4	61.2 ± 9.0	**<0.001**
Weight, kg	79.4 ± 11.8	83.0 ± 14.1	**0.001**	71.9 ± 12.5	78.3 ± 14.2	**<0.001**
Height, cm	169.7 ± 7.1	168.7 ± 7.6	0.094	158.1 ± 6.7	156.0 ± 6.6	**<0.001**
BMI, kg/m^2	27.6 ± 3.8	29.2 ± 4.6	**<0.001**	28.8 ± 5.0	32.3 ± 5.8	**<0.001**
Exercise	140 (52.0)	239 (43.9)	**0.029**	203 (36.1)	320 (25.8)	**<0.001**
Smoking status	160 (59.5)	313 (57.5)	0.597	129 (23.0)	221 (17.9)	**0.011**
Comorbidities						
CAD	26 (9.7)	154 (28.3)	**<0.001**	22 (3.9)	165 (13.3)	**<0.001**
DM	49 (18.2)	205 (37.7)	**<0.001**	71 (12.6)	472 (38.1)	**<0.001**
Hyperlipidemia	31 (11.5)	167 (30.7)	**<0.001**	50 (8.9)	317 (25.6)	**<0.001**
Obesity	69 (25.7)	208 (38.2)	**<0.001**	209 (37.2)	772 (62.4)	**<0.001**
Outcome measurements						
Anterior thigh MT (mm)	41.5 ± 7.7	37.7 ± 8.7	**<0.001**	36.2 ± 7.3	34.4 ± 7.9	**<0.001**
STAR	1.52 ± 0.28	1.31 ± 0.30	**<0.001**	1.28 ± 0.28	1.09 ± 0.28	**<0.001**
Grip strength, kg	37.3 ± 8.0	36.1 ± 9.3	**0.048**	24.6 ± 6.1	22.1 ± 6.3	**<0.001**
CST, sec	9.9 ± 3.5	10.3 ± 3.7	0.174	11.1 ± 4.6	12.2 ± 4.8	**<0.001**
Gait speed, m/sec	1.09 ± 0.28	0.97 ± 0.23	**<0.001**	1.09 ± 0.27	0.92 ± 0.26	**<0.001**
Sarcopenia	37 (13.8)	156 (28.7)	**<0.001**	52 (9.3)	304 (24.6)	**<0.001**

Data are presented as mean ± SD or *n* (%).

Statistically significant values are marked as bold.

MT, muscle thickness; STAR, sonographic thigh adjustment ratio.

were informed about study procedures and were enrolled upon written consent. The study protocol was approved by the local ethics committee. This study conforms to all STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines and reports the required information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B685).

Detailed interviews were completed to collect data on sociodemographic characteristics, educational attainment, exercise and smoking habits, presence/duration of chronic comorbidities (e.g., HT, DM, CAD, and hyperlipidemia), and drug use. Body weight and height were measured.

Ultrasonographic Measurements

Using linear probes (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/PHM/B686), anterior thigh muscle thickness (dominant side), was measured at 50% level between the anterior superior iliac spine and the upper pole of patella, while subjects lied in supine position. Adequate amount of gel was used to avoid any compression. During axial imaging, the measurement was taken between the outer fascia of rectus femoris and the periosteum of femur. Relative anterior thigh muscle thickness (i.e., sonographic thigh adjustment ratio) was subsequently calculated by dividing the anterior thigh muscle thickness (in millimeters) by body mass index (BMI).[1,14] All physicians who performed the measurements were experienced enough regarding musculoskeletal ultrasound and they easily adopted the standardized technique for measuring anterior thigh muscle thickness. In addition, before their data were included in the analyses, each and every center was required to send their ultrasound images to be technically approved by the lead center/authors.

Functional Evaluations

Handgrip strength was measured with Jamar dynamometer (baseline hydraulic hand dynamometer, Irvington), which was used at the second handle position. Subjects were instructed to be in the sitting position, with their shoulders adducted and neutrally rotated, elbows flexed at 90 degrees, and forearms/wrists kept in the neutral position. Three repeat measurements were performed from the dominant side and the maximum value obtained was taken for the analysis.

Chair stand test was performed while subjects were asked to (start with) stand up and sit down from a chair without arm rest, for 5 times as fast as possible, with their arms crossed over their chests. Gait speed measurements were performed as subjects were asked to walk at their usual pace over a 6-meter course. The participants were informed to stand with both feet touching the starting line and started walking after the command. The time duration (between beginning and ending) was measured by a chronometer and transformed into meters per second. Three consecutive measurements were performed for both and mean values were taken for the analyses.

Diagnosis of Sarcopenia

The ISarcoPRM algorithm[6] was used for the diagnosis of sarcopenia whereby low muscle mass (i.e., Sonographic Thigh Adjustment Ratio values <1.4 for males and <1.0 for females) was combined with low grip strength (i.e., <32 kg for males and <19 kg for females) and/or increased CST time (≥12 seconds).

Statistical Analysis

Statistical analyses were performed using SPSS version 21 statistical software package. Numerical variables are given as mean ± SD and categorical variables as number and percentages. Normality assumption was tested by Kolmogorov-Smirnov test. Mean value comparisons for numerical variables were performed by Student's *t* test if they were normally distributed (i.e., anterior thigh muscle thickness and Sonographic Thigh Adjustment Ratio values). The other (nonnormally distributed) variables were compared by Mann Whitney *U* test. Comparisons of categorical variables were established using χ^2 analysis. Possible associations among the presence of HT, the use of different antihypertensive drug(s), and sarcopenia-related parameters (i.e., muscle mass, strength, and performance tests) were evaluated through multivariate linear logistic regression analyses—with adjustments for potential confounders including sociodemographic and clinical variables. Statistical significance was set at $P < 0.05$.

RESULTS

Of the 2613 participants (813 males, 31.1%), 1782 (68.2%) were hypertensive (Table 1). Compared with normotensive participants in both sexes, weight and BMI values were higher and presence of all comorbidities including DM, hyperlipidemia, CAD, obesity, and sarcopenia were more frequent in the hypertensive group (all $P < 0.01$). Similarly, all sarcopenia-related measures (except CST in males) were worse in the hypertensive group than in normotensive subjects (all $P < 0.05$).

Sarcopenia was detected in 89 of 831 subjects (10.7%) among normotensive subjects and 460 of 1782 hypertensive patients (25.8%, $P < 0.001$). The median number of antihypertensive drugs was 2 (1–5), and the median duration of HT was 7 yrs (0.3–54 yrs). A total of 707 patients were using a single antihypertensive drug (39.7%), 751 were using a dual antihypertensive drug combination (42.1%), 270 were using a triple antihypertensive drug (15.2%), and the rest ($n = 54$) were using a combination of 4 drugs or more ($n = 3.0\%$).The ACEI was used by 600 individuals (monotherapy = 231), angiotensin II receptor blocker (ARB) was used by 765 individuals (monotherapy = 166), and other antihypertensive drugs were used by 417 subjects (β-blockers only, $n = 128$; calcium-channel blockers [CCBs] only, $n = 165$; diuretics only, $n = 18$).

The frequency of sarcopenia among normotensive and hypertensive participants (using different antihypertensive drugs) according to age ranges is given in Figure 1. Likewise, normal muscle mass with decreased muscle function (i.e., grip strength and/or CST performance) was detected in 223 (26.8%) normotensive and 443 (24.9%) hypertensive participants. In hypertensive males, sarcopenia was detected in 56 of 218 patients (25.7%) using ACEIs, 74 of 209 (35.4%) using ARBs, and 28 of 122 (23.0%) using other drug(s) (i.e., CCBs, β-blockers, diuretics, and α-blockers, $P = 0.023$). In hypertensive females, sarcopenia was detected in 92 of 393 patients (23.4%) using ACEIs, 134 of 554 ARBs users (24.2%), and 79 of 293 (27.0%) using other drug(s) ($P = 0.540$).

When sociodemographic/clinical characteristics and other potential confounders were tested in binary logistic regression

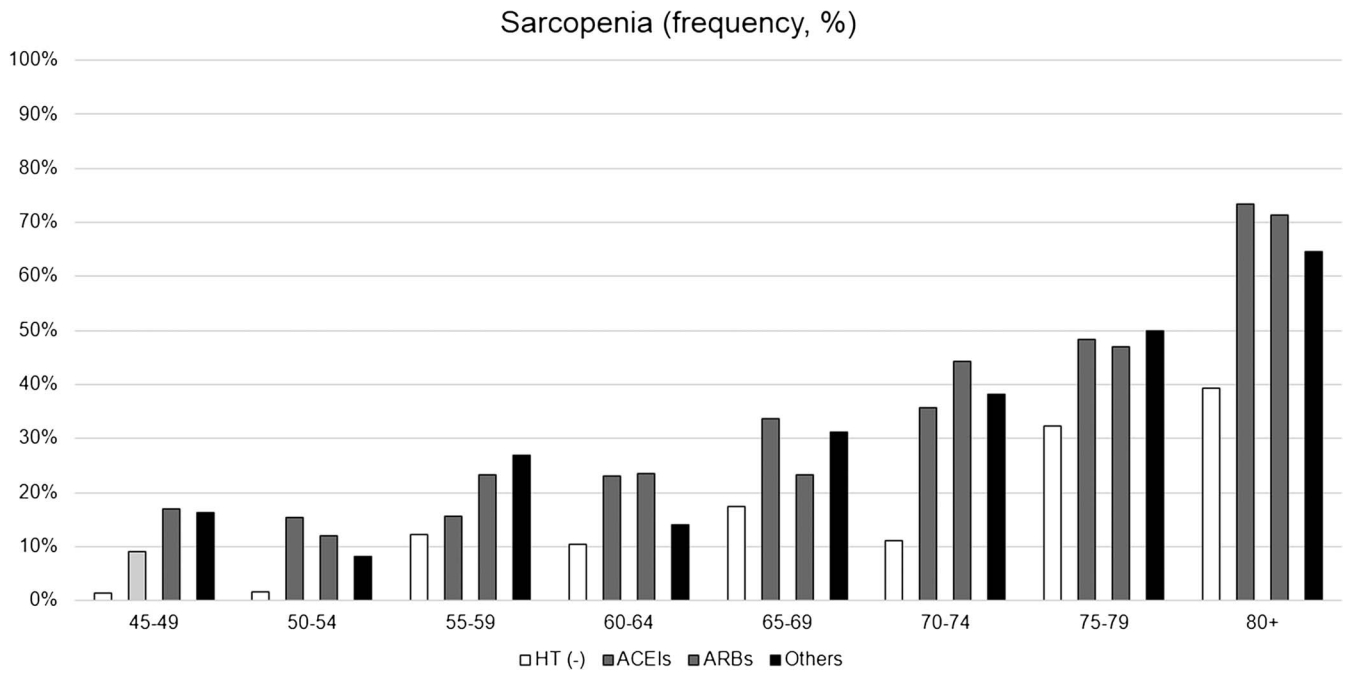

FIGURE 1. Frequency of sarcopenia among normotensive subjects and hypertensive patients (using different antihypertensive drugs) according to age ranges (in years).

analyses (Table 2), presence of HT was found to be an independent predictor of sarcopenia both in males (odds ratio [OR] = 2.403 [95% confidence interval {CI} = 1.514–3.813]) and females (OR = 1.906 [95% CI = 1.328–2.734], both $P < 0.001$).

Adjusting for potential confounding factors in multivariate linear regression analyses (Table 3), we found that all sarcopenia-related measures (except grip strength and CST in males) were independently and negatively related to HT (all $P < 0.05$). Table 4 shows multivariate linear regression analyses concerning independent associations among the use of ACEIs, ARBs, or other drugs and sarcopenia-related tests/measures among hypertensive patients. In females, when compared with those using ARBs, ACEIs users had higher grip strength and CST performance values but had lower muscle thickness (also in males) and gait speed values (all $P < 0.05$). Furthermore, in female patients, when compared with those using other antihypertensive drugs, ACEIs users had higher grip strength and CST performance, while ARBs users had lower grip strength values (all $P < 0.05$).

DISCUSSION

In light of our results; the diagnostic criteria for sarcopenia, that is, anterior thigh muscle thickness and gait speed, grip strength, and CST performance (only in females) were significantly different between normotensive and hypertensive groups. Similarly, HT independently increased the risk of sarcopenia both in males (approximately 2.5 times) and females (approximately 2 times).

Hypertension was negatively associated with the sarcopenia-related parameters (except grip strength and CST in males). In addition, in male patients using ARBs, we found the highest

TABLE 2. Binary logistic regression analyses for predicting sarcopenia ($N = 2613$)

	Male			Female		
	β	CI	*P*	β	CI	*P*
Age	1.089	1.066–1.112	**<0.001**	1.060	1.044–1.077	**<0.001**
Weight	1.019	0.996–1043	0.114	1.045	1.030–1.059	**<0.001**
Height	0.961	0.928–0.995	**0.025**	0.940	0.917–0.963	**<0.001**
Education	0.720	0.617–0.840	**<0.001**	0.852	0.752–0.964	**0.011**
Exercise	0.877	0.711–1.081	0.219	0.795	0.649–0.973	**0.038**
Smoking	0.672	0.460–0.981	**0.039**	0.671	0.461–0.977	**0.038**
DM	1.514	1.032–2.223	**0.034**	0.885	0.668–1.172	0.392
Hyperlipidemia	0.669	0.426–1.053	0.082	1.045	0.762–1.433	0.785
CAD	0.892	0.561–1.421	0.631	1.210	0.822–1.780	0.334
Obesity	1.065	0.598–1.895	0.831	0.946	0.632–1.416	0.787
Hypertension	2.403	1.514–3.813	**<0.001**	1.906	1.328–2.734	**<0.001**

Statistically significant values are presented in bold.

TABLE 3. Multivariate linear regression analyses for the association (β) between hypertension and sarcopenia-related measures (N = 2613)

	Muscle Thickness		Grip Strength		Chair Stand Test		Gait Speed	
	Male	Female	Male	Female	Male	Female	Male	Female
Age, yr	−0.124[a]	−0.212[a]	−0.423[a]	−0.222[a]	0.354[a]	0.243[a]	−0.168[a]	−0.264[a]
Weight, kg	0.383[a]	0.204[a]	0.216[a]	0.157[a]	0.065	0.082[b]	0.046	−0.216[a]
Height, cm	−0.039	0.038	0.162[a]	0.176[a]	0.060	0.118[a]	0.165[a]	0.193[a]
Education	0.093[c]	−0.057[b]	0.093[c]	0.130[a]	−0.072[b]	−0.177[a]	0.070[b]	0.042
Exercise	0.035	0.051[b]	0.065[b]	0.093[a]	−0.116[a]	−0.131[a]	0.084[b]	0.060[c]
Smoking	0.041	0.119[a]	0.042	0.001	−0.024	0.026	0.001	−0.018
DM	−0.052	0.002	−0.078[c]	−0.051[b]	0.089[c]	−0.001	−0.072[b]	−0.023
Hyperlipidemia	0.015	−0.062[b]	0.033	0.001	−0.071[b]	−0.008	−0.020	−0.027
CAD	0.016	−0.021	−0.020	−0.015	0.018	−0.021	−0.050	−0.068[c]
Obesity	−0.015	0.074[b]	−0.047	−0.006	0.019	−0.039	−0.088	0.055
Hypertension	−0.237[a]	−0.116[a]	−0.043	−0.128[a]	0.029	0.055[b]	−0.111[c]	−0.125[a]
n	813	1800	813	1800	813	1800	813	1800
R	0.463	0.407	0.615	0.503	0.398	0.376	0.394	0.486
R^2	0.213	0.165	0.378	0.253	0.159	0.141	0.155	0.236

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.
R, correlation coefficient; R^2, coefficient of determination.

frequency of sarcopenia (35.4%) compared with patients using ACEIs and other antihypertensive drugs and the female sex (between 23.0% and 27.0%).

The relationship between skeletal muscle mass and HT has been investigated in some clinical studies.[15–18] In one/previous study (n = 2172), appendicular muscle mass measured by dual-energy x-ray absorptiometry was found to have negative correlation with mean systolic blood pressure.[16] In another large cross-sectional study (n = 4846) using the same method and adjusting for potential confounders, muscle mass was revealed as a risk factor for HT in older adults.[17] In contrary, a large Korean prospective cohort study (n = 132,324) demonstrated that low relative skeletal muscle mass measured by bioelectrical impedance analysis was independently associated with the incidence of HT only in men.[18] Lack of correlation among Korean women might have been due to the measurement method (i.e., bioelectrical impedance analysis), which—despite its convenience—is not considered to be the prompt tool for skeletal muscle mass

TABLE 4. Multivariate linear regression analyses for investigating the potential associations (β) between different antihypertensive drugs and sarcopenia-related parameters in hypertensive patients (n = 1782)

	Muscle Thickness		Grip Strength		Chair Stand Test		Gait Speed	
	Male	Female	Male	Female	Male	Female	Male	Female
ACEIs vs. ARBs[a]	−0.095[b]	−0.097[c]	0.063	0.167[d]	−0.064	−0.123[d]	−0.032	−0.098[c]
n	436	955	436	955	436	955	436	955
R	0.444	0.429	0.609	0.460	0.439	0.378	0.440	0.376
R^2	0.197	0.184	0.370	0.211	0.193	0.143	0.193	0.141
ACEIs vs. others[a]	−0.093	−0.033	−0.059	0.137[d]	−0.069	−0.109[c]	0.030	−0.021
n	332	683	332	683	332	683	332	683
R	0.471	0.419	0.641	0.456	0.518	0.448	0.433	0.450
R^2	0.221	0.175	0.410	0.208	0.268	0.200	0.187	0.203
ARBs vs. others[a]	0.035	0.059	−0.131[b]	−0.068	0.048	0.001	0.065	0.045
n	314	836	314	836	314	836	314	836
R	0.431	0.400	0.629	0.478	0.342	0.335	0.378	0.387
R^2	0.186	0.160	0.396	0.228	0.117	0.112	0.143	0.150

[a] The variables were adjusted for age, body weight, height, doing exercise, educational attainment, smoking status, presence of comorbidities (i.e., DM, hyperlipidemia, CAD, and obesity), duration of HT and number of antihypertensive drugs used.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.001$.
R, correlation coefficient; R^2, coefficient of determination.

assessment.[18] Being in line with the previously mentioned two studies, we detected a negative relationship between the presence of HT and muscle mass. The major added value of our study would be the use of multiple indices for evaluating sarcopenia, that is, grip strength, CST, gait speed, and anterior thigh muscle mass where age-related muscle loss is the most common/evident. Of note, the mechanism of muscle mass loss in HT and other RAS-related disorders such as obesity, DM, hyperlipidemia, and CAD has been widely investigated.[4–6] In short, HT overactivates the classical RAS pathway, which in turn leads to increased Ang-II levels and, accordingly, skeletal muscle atrophy.[4,5,19,20]

Besides RAS-related disorders, age, body weight, height, smoking status, obesity, and exercise habits have all been found to be associated with skeletal muscle mass.[21] In this study, we found that anterior thigh muscle thickness was negatively correlated with age but positively with weight in both sexes. It had also negative associations with education and hyperlipidemia but positive associations with exercise, obesity, and smoking in females. Although muscle thickness was suggested to be associated with age- and RAS-related disorders,[4,7] the highest correlations were found with HT in both sexes. Our results are in line with the current literature, except for the association with smoking. The detected positive association with smoking in females might have been biased by the cross-sectional nature of the study, whereby higher frequency of smoking among relatively healthier participants might have also biased our analyses.

Muscle atrophy in hypertensive patients and in those with other age-related chronic metabolic disorders can lead to decreased muscle function, as measured by grip strength, CST performance, and gait speed. A longitudinal cohort study of 22-yr follow-up (n = 963) has reported that lifestyle factors and chronic conditions such as marked weight loss, becoming physically sedentary, smoking, and/or presence of cardiovascular disease, DM, and HT were related to accelerated decline of handgrip strength.[22] Furthermore, over a 9-yr-data from UK biobank (n = 44,315) revealed an increased risk of decline in grip strength among patients living with multimorbidity (≥2 comorbid conditions) and among those with lifestyle risk factors (e.g., physical inactivity, overweight, and obesity).[21] On the contrary, over a 27-yr follow-up in Japanese-American men (n = 3741), HT was found to be related to lower risk of accelerated grip strength decline.[23] Contradictory findings may, at least partially, be caused by variations in subjects' physical stature. Although body weight and height are individually correlated with grip strength, higher weight/BMI ratio is a risk factor for HT.[23] Another explanation for conflicting results might be other nonstudied/understudied confounders. In our study, a comprehensive list of confounders was evaluated; yet, low R^2 values of final models suggest remnant confounders/predictors of sarcopenia.

In our study, HT was found to be significantly correlated with grip strength and CST (only in females) and gait speed in both sexes. In addition, grip strength was related to age, weight, height, education level, exercise, and presence of DM in both sexes. The CST performance was negatively correlated with age and positively correlated with education and exercise in both sexes. Gait speed was negatively correlated with age in both sexes and with weight and CAD in females. Moreover, gait speed showed positive correlations with height and exercise in both sexes. To our best knowledge, this is the first study investigating the relationships of RAS-related disorders and physical stature with the diagnostic criteria of sarcopenia in the middle-aged and older adults, and simultaneously comparing all four diagnostic indices of sarcopenia. In the hitherto literature on the relationship between sarcopenia and chronic metabolic disorders (especially HT), the used diagnostic criteria are not consistent. In some of them, loss of muscle mass without muscle dysfunction was considered as sarcopenia. Herewith, the diagnosis of sarcopenia needs to be established with low muscle mass as well as low muscle function (i.e., grip strength and/or CST). In our study, sarcopenia was observed more common in hypertensive (28.7%) versus normotensive (24.6%) males (13.8%) and females (9.3%). Supporting our findings, a recent preliminary study of 272 middle-aged and older adults revealed that sarcopenia was more prevalent in hypertensive (32.2%) than normotensive (7.8%) subjects.[7] Prevalence of HT is found to be more common in sarcopenic patients than their nonsarcopenic peers.[15] A recent study—evaluating the predictors of sarcopenia among 99 variables by using machine learning—found age, systolic arterial HT, and number of the chronic diseases as independent predictors of sarcopenia.[20] In most of the published work, presence of sarcopenia was based on the diagnostic criteria using appendicular muscle mass measurements. As significant loss of muscle mass primarily initiates in the anterior thigh, it is more rational to focus on this region rather than the appendicular ones for early/accurate diagnosis of sarcopenia.[14,15,24–27] Therefore, we used a very recent/novel algorithm based on the anterior thigh muscle measurements.[1]

It is important to emphasize that decline in muscle function is not only dependent on the loss of muscle mass but also prone to deteriorative effects of chronic metabolic disorders and age on cognition and neuromotor control.[4] These effects might be linked to RAS activity and/or resulting structural abnormalities in brain.[14] Cognitive dysfunction and neuromotor impairment may be the main causes of decline in muscle function and physical performance in older patients with normal muscle mass. In this regard, it has been found that cognitive impairment as well as multimorbidity, depression, smoking, and physical inactivity were revealed to be related to poor performance in CST.[28] Subclinical white matter lesions and small brain infarcts can also be related to decreased grip strength, CST performance, and gait speed in older adults, possibly due to aging, HT, and carotid artery atherosclerosis.[29–31] In our study, the proportion of participants with normal muscle mass but decreased muscle function (as measured by grip strength and CST performance) were 26.8% and 24.9% among normotensive and hypertensive subjects, respectively.

Importantly, we compared the use of different antihypertensive drugs in an attempt to detect their relationship with sarcopenia parameters. In male patients using ARBs, we found the highest frequency of sarcopenia (35.4%) compared with patients using ACEIs and other antihypertensive drugs and the female sex. Of note, ARB use seems to related to higher muscle mass and gait speed values, whereas ACEIs are more likely to be related to higher muscle function only in female patients with HT. Having significant effects of ACEIs and ARBs on sarcopenia-related parameters only in female patients might be caused because of the following reasons. First, the number of male hypertensive patients (n = 544) seems to be a distinctly important factor than the female patients (n = 1238). Hence, it might not have reached statistical significance (type 2 error) because these numbers decreased further when paired comparisons were made by dividing them into three subgroups (ACEI,

ARB, and others) according to antihypertensive drug usage. In addition, male patients with HT had better muscle function and physical performance parameters, and higher frequency of regular exercise (43.9% vs. 25.8%), lower BMI values, and obesity frequency (38.2% vs. 62.4%) might have led to insignificant results.

The use of ACEIs has also been investigated for the treatment of sarcopenia. Although some studies have shown promising results, others reported no association—possibly due to variations in methodologies, including heterogeneity in patient populations, outcome measurements, duration of intervention, and/or combinations of antihypertensive drugs.[4] In a 3-yr longitudinal cohort of the Women's Health and Aging study ($n = 641$), continuous users of ACEIs for the treatment of HT showed a lower 3-yr decline in knee extension strength and gait speed compared with continuous/intermittent users of other antihypertensive drugs (namely, β-blockers, CCBs, thiazides, or α-blockers) and those without medication.[8] A cross-sectional study of Health ABC in community-dwelling well-functioning older adults ($n = 2431$) has shown that ACEI use was related to larger lower extremity muscle mass compared with the use of β-blockers, CCBs, and thiazides.[9] Another recent cross-sectional study in community-dwelling older adults ($n = 1567$) on the relationship between antihypertensive drug use (i.e., diuretics, CCBs, β-blockers, and ACEIs or ARBs) and physical function has shown that the use of β-blockers and 3 antihypertensives or more were related to higher sedentary time.[32] Conflicting results might probably be due to heterogeneity in selected populations and measurement techniques (for muscle mass/function), with comprehensiveness of adjustments for confounding factors.

The main limitation of our study is its cross-sectional design. In addition, there were many antihypertensive drug combinations, and the number of patients using drugs other than RAS blockers was not sufficient. Given that some patients might have changed their antihypertensive medications and/or started additional drugs over the years, interactions and/or carry-over effects can therefore not be excluded. Although we have focused on HT, the presence of other comorbid diseases and the use of other drugs (e.g., statins, oral antidiabetic drugs, or insulin) might have led to sarcopenia as well. Moreover, we did not measure the cognitive function of our participants, yet, integration of cognitive function in future studies would contribute to better evaluation of the effect of HT on muscle function and physical performance. Multivariate regression analyses were actually used to adjust for such confounders and/or to control for their effects of other predictors of sarcopenia.

By using a novel algorithm based on anterior thigh (rather than appendicular) muscle mass measurements to confirm the diagnosis of sarcopenia, we determined that the presence of HT was negatively related to the sarcopenia-related parameters and increased the risk of sarcopenia at least 2 times among middle-aged and older adults. Among hypertensive drugs, while ACEIs seem to be related to more favorable effects on muscle function, ARBs present positive effects on muscle mass and physical performance only in females. Further longitudinal studies in larger populations are warranted for investigating the effects of different antihypertensive drugs regarding the diagnostic criteria for sarcopenia.

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