Reassessing Sarcopenia In Hypertension: STAR and ACE Inhibitors Excel

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Abstract

Background: Hypertension and sarcopenia are commonly seen in older adults. The renin-angiotensin system and the therapeutic use of angiotensin converting enzyme (ACE) inhibitors have been on the agenda of sarcopenia in different perspectives. Our aim was to explore the frequency of sarcopenia in patients with hypertension and to investigate the association between the use of ACE inhibitors and sarcopenia. Methods: A total of 233 community dwelling adults were recruited. Anterior thigh muscle thickness was measured by ultrasound. Handgrip strength, gait speed and chair stand test were evaluated. Presarcopenia was diagnosed in the presence of low sonographic thigh adjustment ratio (STAR) values and sarcopenia was diagnosed if low STAR values were coupled with low functional tests. Results: 109 subjects (46.8%) had no comorbid disease; 93 (75.0%) had one, 21 (16.9%) had two, eight (6.5%) had three and two (1.6%) had four comorbid diseases. Both presarcopenia (48.3% vs. 21.1%) and sarcopenia (33.3% vs. 7.0%) were more commonly seen in hypertensive when compared to normotensive older adults. Subgroup analysis of older adults with hypertension revealed that sarcopenia was less prevalent (p=0.020) in patients using ACE inhibitors (9.1%) than those using angiotensin receptor blockers (ARBs) (40.5%) and other antihypertensive drugs (42.9%). After binary logistic regression analyses; only the presence of hypertension seemed to independently predict the development of sarcopenia in older adults [OR=7.9 (95% CI: 2.6-24.5, p<0.001)]. Conclusions: Sarcopenia is highly prevalent in hypertensive older adults. Among many antihypertensive medications, ACE inhibitors seem to have favorable effects on both disorders.

What's already known about this topic?

Hypertension and sarcopenia are commonly seen in older adults. Renin-angiotensin system activation may contribute to the development of both sarcopenia and hypertension.

What does this study add?

The presence of hypertension independently increased the risk of sarcopenia in older adults. The use of angiotensin converting enzyme inhibitors for hypertension appeared to be preventive against the development of sarcopenia.

INTRODUCTION

By and large, the population is getting older; and physicians unavoidably/undoubtedly become exposed to problems of older adults in daily practice. Hypertension and sarcopenia appear to be such/two commonplace

problems in this sense. The former is one of the most prevalent disorders that cause cardiovascular disease and mortality, and its prevalence (overall about 45%) reaches >60% in >60 years old adults.[1,2] The latter - age-related loss of muscle mass and function - is also a global public health problem in older adults i.e. with a prevalence of 10% in [?]60 years old.[3]

In recent years, a possible 'cross-talk' between the two aforementioned disorders has increasingly been reported. Particularly, the renin-angiotensin system (RAS) and the therapeutic use of angiotensin converting enzyme (ACE) inhibitors have been the main concerns for exploring whether sarcopenia is more prevalent in hypertensive individuals and/or various antihypertensives might impact sarcopenia in different ways. Herein, the RAS is a major regulator of blood pressure and it also regulates muscle mass.[4] As such, the presence of an active classical RAS axis exerts deleterious effects not only on the cardiovascular system but also on the skeletal muscles. Yet, increased levels of angiotensin II (Ang-II) are known to cause several conditions like insulin resistance, atrophy and fibrosis of muscles.[4]

On the other hand; either due to the use of different techniques to define sarcopenia or the complexity of hypertension treatment, the pertinent literature is quite heterogenous as well as inconclusive. Accordingly, the purpose of this study was two-fold; first we tried to explore the frequency of sarcopenia in patients with hypertension, and second, we aimed to investigate the association between the use of ACE inhibitors and sarcopenia. In this regard, we have used a novel/robust approach to detect early/regional muscle loss i.e. anterior thigh muscle mass measurements for prompt diagnosis of sarcopenia.[5]

METHODS

Participants

A total of 230 community dwelling adults ([?]45 years old) who were admitted to the physical and rehabilitation medicine outpatient clinic of a tertiary care university hospital were recruited. Subjects who had neuromuscular or rheumatic diseases, history of major orthopedic surgery and mobility limitations were excluded from the study. All participants were informed about the study procedure and subjects were enrolled if they consented to participate. The local ethics committee approved the study protocol.

Demographic data, smoking status, comorbidities (e.g. hypertension, diabetes mellitus, chronic cardiovascular/pulmonary disease) and drug usage were noted. Weight, height and waist/hip circumferences were measured to the nearest 0.1 kg and 1 cm.

Ultrasonographic measurements

Anterior thigh muscle thickness was measured by using a 5-12 MHz linear probe (Logiq P5, GE, Medical Systems, USA). Ultrasound (US) images were obtained without any compression by using adequate amount of gel, while subjects lied in supine position. The muscle thickness was measured in the axial view - at 50% level between the anterior superior iliac spine and upper pole of the patella. The measurement was taken between the outer fascia of rectus femoris and the periosteum of femur (Fig. 1). All measurements were performed (from the dominant side) by a physiatrist (MK) who is an expert in musculoskeletal US - with more than 10 years of experience. Thereafter, sonographic thigh adjustment ratio (STAR) was calculated via dividing the anterior thigh muscle thickness (mm) by body mass index (BMI).[5]

Grip strength and performance evaluation

Handgrip strength was measured with Jamar dynamometer (Baseline Hydraulic Hand dynamometer Irvington, NY, USA), which was used at the second handle position. The subjects were instructed to be in sitting position as their shoulders were adducted and neutrally rotated, elbows were flexed at 90°, and the forearms/wrists were kept in neutral position. For performance evaluations; chair stand test (CST) was performed while subjects were asked to stand up and sit down from a chair without arm rest for five times, with their arms crossed over their chests.[6] For gait speed measurements, 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 to start walking after the command. Time duration (between beginning and ending) was measured by

a chronometer and transformed into meter/second. Three measurements for all the performance tests were obtained and the mean values were taken into analyses.

Sarcopenia diagnosis

Presarcopenia was diagnosed in the presence of low STAR values; whereas sarcopenia was diagnosed if low STAR values were coupled with low muscle strength and/or low physical performance as well.[7] The cut-off values were respectively taken as 1.0 and 1.4 for STAR;[5] 19 kg and 32 kg for grip strength in males and females.[8] The cut-off values were 1.00 m/sec for gait speed and 12 sec for CST in both genders.[9]

Statistical analysis

Statistical analyses were performed using SPSS 23. Numerical variables are presented with mean±SD. Normal distribution was tested by Kolmogorov-Smirnov test if the sample size was larger than 50; otherwise the Shapiro-Wilk test was used. Mean value comparisons for numerical variables were done by Student t or Mann Whitney U tests; while categorical variables were compared by chi-square or Fisher exact tests, as appropriate. Variables which were considered to affect the presence of sarcopenia were taken into binary logistic regression analysis using the stepwise method (backward selection). The evaluation of the model adjustment and adequacy was obtained by Hosmer and Lemeshow tests.[10] Statistical significance was set at $p<0.05$.

RESULTS

Demographic and clinical data are presented in Table 1. While 109 subjects (46.8%) had no comorbid disease; 93 (75.0%) had one, 21 (16.9%) had two, eight (6.5%) had three and two (1.6%) had four comorbid diseases. Age and waist circumference were similar between the genders (both $p>0.05$). While BMI and hip circumference were lower, anterior thigh muscle thickness was higher in males as compared to females (all $p<0.001$). The presences of hypertension, diabetes mellitus, chronic lung disease, presarcopenia and sarcopenia were similar between the genders (all $p>0.05$). However, the frequencies of coronary artery disease and smoking were more in males than in females (both $p<0.05$). Additionally, males had better grip strength and performance test (i.e. CST and gait speed) values than females (all $p<0.001$).

Comparisons of the clinical data regarding hypertension are given in Table 2. 28.7% of hypertensive patients (31 out of 108) and 3.2% of normotensive subjects (four out of 125) had sarcopenia ($p<0.001$). In middle-aged adults; the presence of diabetes mellitus and low physical performance (i.e. CST and gait speed) were more frequent in hypertensive vs. normotensive subjects (all $p<0.05$). In older adults; the presence of diabetes mellitus, coronary artery disease, low CST, presarcopenia and sarcopenia were more frequent in hypertensive vs. normotensive subjects (all $p<0.01$). Further, hip circumference was higher in hypertensive vs. normotensive older adults ($p<0.001$). Overall, although statistically insignificant ($p=0.062$), females were more prevalent in the hypertensive older adults.

Subgroup analysis of older adults with hypertension (N=87) revealed that sarcopenia (N=29) was less prevalent ($p=0.020$) in patients using ACE inhibitors (2/22 patients, 9.1%) than those using angiotensin receptor blockers (ARBs) (15/37 patients, 40.5%) and other antihypertensive drugs (i.e. alpha/beta blockers, diuretics, calcium channel blockers) (12/28 patients, 42.9%) (Fig. 2). When age, gender, BMI, and presence of smoking and aforementioned comorbid diseases were taken into binary logistic regression analyses; only the presence of hypertension seemed to independently predict the development of sarcopenia in older adults [OR=7.9 (95% CI: 2.6-24.5, $p<0.001$)].

DISCUSSION

This study showed that both presarcopenia (48.3% vs. 21.1%) and sarcopenia (33.3% vs. 7.0%) were more prevalent in hypertensive when compared to normotensive older adults. Of note, among several parameters, only the presence of hypertension independently increased (almost 8 times) the risk of sarcopenia in older adults. Interestingly, it is noteworthy that the use of ACE inhibitors for hypertension appeared to be preventive against the development of sarcopenia.

A very recent systematic review and meta-analysis investigated the prevalence of sarcopenia in different comorbid diseases whereby sarcopenia was found to be highly prevalent in patients with cardiovascular diseases (31.4%), diabetes mellitus (31.1%), dementia (26.8%), and respiratory disorders (26.8%).[11]Unfortunately, the meta-analysis did not include hypertension - which is actually one of the most frequent problems causing cardiovascular disease. Another recent study (in 166 older adults with a mean age of 77.2 years) evaluated the prevalence of sarcopenia considering 99 variables by using machine learning techniques (a sub-branch of artificial intelligence).[12] In order of importance; age, systolic arterial hypertension, mini nutritional assessment, number of chronic diseases and blood sodium level were reported to be the determinants for sarcopenia.

In previous studies, the relationship between sarcopenia and hypertension has been evaluated according to total muscle mass measurements.[13,14] However, as sarcopenia initially starts at the anterior thigh, it is more reasonable to use those muscle measurements for the diagnosis of sarcopenia whereby the use of total muscle mass loss would easily be misleading.[5,7,15,16]For this reason, we have used anterior thigh (instead of total) muscle measurements which have higher correlations with knee extensor strength and performance tests according to the recent literature.[5] Importantly, we have found that presarcopenia (48.3%) and sarcopenia (33.3%) were highly prevalent in hypertensive older adults.

One possible mechanism to explain this high prevalence (of sarcopenia in hypertension) might be the RAS activation which increases the levels of circulating Ang-II levels - that, in turn, may contribute to the development of both sarcopenia and hypertension.[4] Of additional note, mineralocorticoid receptor activation also causes a progressive loss of heart and skeletal muscle myocytes due to apoptosis in heart failure - called as 'heart cachexia' which is a process resembling sarcopenia.[13,17] Further, hypertension has effects on physical function as well. For instance, like many other cardiovascular diseases, low gait speed has been associated with hypertension.[18] In a 2-year longitudinal study, hypertension was found to be related with lower gait speed at baseline and with higher annual decline in gait speed during follow up.[19] Herein, hypertension can affect the gait speed not only via white matter abnormalities in the central nervous system but also due to atherosclerosis in the peripheral arteries.[19] Likewise, higher handgrip strength was reported to be related with lower risk of hypertension in older females.[20] In our study, while low gait speed was observed to be more common only in middle-aged hypertensive patients, low CST was more prevalent in both middle-aged and older hypertensive patients. However, the frequency of low handgrip strength was not different in either group. Indeed, CST is a test assessing power which is more strongly related with functional performance than muscle strength in the elderly.[21,22] Additionally, power declines at a faster rate than strength by aging.[21]Therefore, CST can be more useful than muscle strength tests for the early detection of sarcopenia.

Active classical RAS axis has deleterious effects on the skeletal muscle; therefore, its inhibition has been important in the treatment of several pathologies affecting the skeletal muscle (e.g. insulin resistance, muscle atrophy, fibrosis etc.).[4] While some of the studies have shown favorable effects; others reported no association in between.[23-26] When we focus on their methodologies, the outcome measures are quite heterogeneous. In this regard; patient population (functionally impaired elderly, high cardiac risk, fall history, hearth failure, or hypertension), performance tests, duration of intervention and follow-up periods, combination of antihypertensive drugs with different exercise protocols, comparison of ACE inhibitors with ARBs or non-ACE inhibitors instead of placebo would be some examples. Additionally, the two most commonly used tests (i.e. grip strength and gait speed) were found to be related with cognition rather than muscle mass. Yet, it is well-known that possible decline in these tests requires long years and therefore treatment effect may not be shown in short periods. Further, high blood pressure can trigger several changes not only in the skeletal muscle, but also in the physical function via cognition.[27]

As mentioned above, the anterior thigh is affected earlier with aging.[16] Therefore, it would be more appropriate to measure anterior thigh muscle mass and strength (by CST or ideally using isokinetic muscle strength testing). Likewise, ACE inhibitors was investigated for the prevention of sarcopenia.[28] In a cohort of the Women's Health and Aging Study, continuous use of ACE inhibitors has been found to exert a favorable impact on gait speed and knee extensor muscle strength after a 3-year follow-up.[23] In the Health, Aging and Body Composition study, patients using ACE inhibitors had higher lower extremity muscle mass than tho-

se using other antihypertensive drugs.[29]Similar to these studies, ACE inhibitors appeared to be preventive against the development of sarcopenia in our study as well; however, we did not observe a similar (preventive) effect concerning the use of ARBs. Herein, a possible explanation would be that ACE inhibitors increase the formation of bradykinin (a potent vasodilator) which promotes muscle blood flow, glucose uptake and hypertrophy via its type 2 receptor.[30,31]

In conclusion, sarcopenia is highly prevalent (1 out of 3) in hypertensive older adults; and among many antihypertensive medications, ACE inhibitors seem to have favorable effects on both disorders. Indisputably, further longitudinal studies in larger populations are awaited also taking into account the contribution of exercise - another common therapy for the two.

Ethical statement: Authors confirm that their study's involvement with human subjects complies with the Declaration of Helsinki.

Author Contributions:

Study concept and design: MK

Acquisition of data: MAC, ÖK, EGK

Analysis and interpretation of data: MK, AMA

Drafting of the manuscript: AMA, TE, FÖ, VR

Critical revision of the manuscript for important intellectual content: LÖ, MK, BK

Approval of final manuscript: MK, AMA, ÖK, MAC, TE, VR, EGK, FÖ, BK, LÖ

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Table 1. Clinical characteristics of the subjects

	All (N=233)	Male (N=75)	Female (N=158)	P*
Age (year)	64.8±10.6	65.4±10.5	64.5±10.7	0.593
BMI (kg/m^2)	28.6±4.6	27.0±3.8	29.4±4.8	<**0.001**
Smoking	21.5	37.3	13.9	<**0.001**
Circumference (cm)				
Waist	99.3±11.8	99.1±12.8	99.7±9.6	0.888
Hip	106.3±8.5	102.8±6.5	108.2±8.8	<**0.001**
Presence of comorbidities				
Hypertension	46.4	40.0	49.4	0.180
Diabetes mellitus	13.7	14.7	13.3	0.776
Chronic lung disease +	10.0	12.0	8.9	0.453
Coronary artery disease	4.7	9.3	2.5	**0.041**
Atrial fibrillation	4.3	4.0	4.4	1.000
Muscle thickness (mm)				
Anterior thigh	37.6±9.4	41.0±9.4	36.0±9.0	<**0.001**
Functional tests				
Chair stand test (sec)	12.7±3.8	10.9±1.9	13.7±4.2	<**0.001**
Grip strength (kg)	26.5±10.1	37.2±8.5	21.4±5.8	<**0.001**
Gait speed (m/sec)	1.13±0.27	1.26±0.26	1.06±0.25	<**0.001**
Presarcopenia	25.3	33.3	21.5	0.053
Sarcopenia	15.0	12.0	16.5	0.374

Data is given as mean±SD or percentage (%).

BMI; body mass index

*p between males and females, and statistically significant variables are shown as bold.

+Including bronchial asthma (N=17) and chronic obstructive pulmonary disease (N=6)

Table 2. Comparison of the clinical data (hypertensive vs. normotensive)

	Aged 45 - 65 years	Aged 45 - 65 years	P	Aged [?]65 years	Aged [?]65 years
	HT (+)	**HT (-)**		**HT (+)**	**HT (-)**
Number	21	68		87	57
Age (year)	55.6±6.3	52.8±5.1	0.074	71.9±6.0	71.6±5.9
Gender, male	23.8	29.4	0.618	29.9	47.4
BMI (kg/m^2)	30.1±4.7	29.0±4.1	0.409	28.7±4.9	27.5±4.7
Smoking	9.5	26.5	0.139	24.1	15.8

	Aged 45 - 65 years	Aged 45 - 65 years	P	Aged [?]65 years	Aged [?]65 years
Circumference (cm)					
Waist	102.0±9.1	99.5±9.9	0.517	100.4±.12.7	96.6±13.1
Hip	107.8±9.2	106.2±7.4	0.511	108.1±9.7	103.5±6.5
Comorbidities					
DM	23.8	5.9	**0.031**	24.1	3.5
CLD+	0.0	1.5	1.000	13.8	17.5
CAD	4.8	0.0	0.236	11.5	0.0
AF	0.0	0.0	N/A	10.3	1.8
Functional tests					
Low CST	33.3	4.4	**0.001**	59.8	33.3
Low grip strength	9.5	19.1	0.506	37.9	38.6
Low gait speed	47.6	10.3	**<0.001**	42.5	31.6
Presarcopenia	9.5	4.4	0.588	48.3	21.1
Sarcopenia	9.5	0.0	0.054	33.3	7.0

Data is given as mean±SD or percentage (%)

BMI; body mass index HT; hypertension, DM; diabetes mellitus, CLD; chronic lung disease, CAD; coronary artery disease AF; atrial fibrillation CST; chair stand test, N/A; not applicable

*Statistically significant variables are shown as bold

+Including bronchial asthma (N=17) and chronic obstructive pulmonary disease (N=6)

FIGURE LEGENDS

Figure 1. Axial ultrasound images (over the anterior thigh) in a 66-year-old male (BMI: 24.7 kg/m^2) (**A**) vs. a 65-year-old female (BMI: 30.2 kg/m^2) (**B**).

$\text{STAR}_{\text{male}} = 44.2/24.7 = 1.79$ (normal >1.4), $\text{STAR}_{\text{female}} = 29.9/30.2 = 0.99$ (normal >1.0).

BMI: Body mass index, d; dermis, sc; subcutaneous fat tissue, F; femur.

Figure 2. Graph showing the frequency of sarcopenia among older adults

*Other antihypertensive drug user, ACEİ; using angiotensin converting enzyme inhibitors, ARBs; using angiotensin receptor blockers

- A significant difference was observed among all the four groups (p<0.001), or among the three hypertensive groups (p=0.020)
- No significant difference was observed between the normotensive subjects and ACEi users, or between ARB and other antihypertensive drug users (both p>0.05).