Cortical Thickness and White Matter Hyperintensity Changes Are Associated With Sarcopenia in the Cognitively Normal Older Adults

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Objective We aimed to explore the impact of sarcopenia on the cortical thickness, white matter hyperintensity (WMH), and subcortical volumes in the cognitively normal older adults.

Methods Sixty cognitively normal older adults with and without sarcopenia were enrolled in the study. They underwent T1 and FLAIR magnetic resonance imaging. Information on muscle mass, muscle strength and muscle function were measured using bioelectrical impedance analysis, handgrip strength and 5 time-chair stand test (CST) respectively. Structural magnetic resonance images were analyzed and processed using Freesurfer v6.0.

Results Compared to the control group, the sarcopenia group demonstrated reduced cortical thickness in left superior frontal, precentral, right post central, inferior parietal, rostral middle frontal superior parietal and both lateral occipital and paracentral gyrus. Volumes of left hippocampus, and periventricular WMH were also reduced in the Sarcopenia group. In addition, we found a significant positive correlation between the left precuneus thickness and muscle mass. Periventricular WMH volumes were also positively correlated with the 5CST score.

Conclusion Sarcopenia affects cortical and subcortical structures in the cognitively normal older adults. These structural changes might be associated with underlying neurobiological mechanisms of sarcopenia in the cognitively normal older adults.

Keywords Sarcopenia; Cortical thickness; White matter hyperintensity; Magnetic resonance imaging; Elderly.

INTRODUCTION

Sarcopenia is defined as loss of muscle mass, decrease in muscle strength and muscle function, which ultimately result in low physical performance, disability, and decreased quality of life. In addition to physical symptoms, sarcopenia is known to be related to cognitive dysfunction in the elderly population. A recent longitudinal study showed that muscle function was associated with incident Alzheimer’s dementia (AD), mild cognitive impairment (MCI), and cognitive decline with and without lean muscle mass. Other studies reported that cognitive changes were related to poor muscle brain axis mediated by an imbalance in myokine secretion. Although previous studies suggested poor muscle functions such as low gait speed and reduced grip strength might be associated with brain atrophy promoting cognitive decline, precise roles of muscle mass and function on the brain structures are not yet clear.

To date, several prior works showed associations between brain structures and sarcopenia in terms of muscle function and mass. A longitudinal study by Rosano et al. found subtle total brain volume abnormalities predicted gait speed decline, but no significant link has been reported between handgrip strength and total brain volume. Another study showed that muscle strength was related to left hippocampal volume ratio in moderate AD patients even after adjusting for age and cognitive status. In terms of white matter (WM) changes, a previous study showed increased total and periventricular...
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(PV) white matter hyperintensity (WMH) burden and progression of PV WMH burden were associated with decreased gait performance over time, while progression of subcortical WMH volume was associated with memory decline in cognitively intact elderly. On the other hand, there have been relatively few studies showing the relationship between muscle and the brain structures. Although not pure muscle mass, Burns et al. reported that lean mass was positively associated with total brain volume in participants with early AD and controls without dementia, and that association was largely driven by WM volume. A recent previous large longitudinal study with 1,284 cognitively normal participants showed that significantly greater atrophy in parietal area was observed in the sarcopenia group compared with the control group. They also found that low muscle mass, not muscle strength, was an independent factor associated with a decrease of gray matter (GM) volume in a joint regression model. Although they suggested that patients with sarcopenia showed GM volume reductions in the frontal, temporal, and parietal regions and in the subcortical structures when compared with the controls, the results were sometimes rather inconsistent. These might be attributable to the methodological issue of brain imaging analysis. Indeed, nearly all previous studies have only investigated total brain or lobar volumes in comparison between the patients with sarcopenia and the healthy controls. It is possible that volumetric study measuring total and lobar volumes is not sufficiently sensitive to assess subtle changes in brain structures. In general, simple volumetric measurement of GM may be less sensitive for subtle brain structural changes than those that disentangle cortical thickness and surface area.

To the best our knowledge, there have been no studies to explore cortical thickness change in patients with sarcopenia. In this study, we tried to explore the cortical thickness and subcortical volumes of sarcopenia patients to overcome the aforementioned problems of the simple volumetric measurements. Through the aforementioned approach, we sought to unravel the distinctive neuronal substrates of the sarcopenia with muscle mass, strength, function, and their clinical implications.

METHODS

Subjects
Thirty cognitively normal elderly subjects with sarcopenia and 30 age-sex matched controls without sarcopenia were included in this study. They were recruited from the normal control volunteers of the Department of Family Medicine, the Saint Vincent’s Hospital, The Catholic University of Korea from 2016 to 2020. The diagnostic criteria of the normal cognition were as follows: 1) subjects aged ≥60 years; 2) Mini-Mental Status Examination score ≥27; 3) Clinical Dementia Rating (CDR)=0. Sarcopenia was defined according to the Asian Working Group for Sarcopenia (AWGS) algorithm, in which the patient has low muscle mass, and low muscle strength or low physical performance. As suggested by the AWGS, low muscle mass was defined as an appendicular skeletal muscle mass (ASM), appendicular skeletal mass index (ASMI, ASM/height²) of <7.0 kg/m² in males and <5.7 kg/m² in females. Low muscle strength was defined as a grip strength of <28 kg in males and <18 kg in females; and low physical performance, 5 time-chair stand test (5CST) ≥12 seconds.

The cognitive functions of the subjects were evaluated with the Korean version of Consortium to Establish a Registry for Alzheimer’s Disease (CERAD-K), which assess the following cognitive domains: verbal fluency, 15-item Boston Naming Test (BNT), the Korean version of Mini-Mental Status Examination (MMSE-K), constructional praxis (CP), word list memory (WLM), word list recall (WLR), word list recognition (WLRc), and constructional recall (CR). The study was conducted in accordance with the ethical and safety guidelines set forth by the local Institutional Review Board of the Catholic University of Korea and written informed consent was obtained from all study subjects. The local Institutional Review Board of The Catholic University of Korea approved this study (No. VC22RISI0118) following the principles set forth by the Declaration of Helsinki.

MRI acquisition
MRI acquisition Imaging data were collected at the Department of Radiology, St Vincent’s Hospital, The Catholic University of Korea, using a 3T Siemens Verio machine and eight channel Siemens head coil (Siemens Medical Solutions, Erlangen, Germany). The parameters used for the T1-weighted volumetric magnetization-prepared rapid gradient echo scan sequences were echo time (TE)=2.5 ms, repetition time (TR)=1,900 ms, inversion time (TI)=900 ms, field of view (FOV)=250 mm, matrix=256×256, and voxel size=1.0×1.0×1.0 mm³. Fluid attenuated inversion recovery (FLAIR) MRI sequences were as follows: TE=135 ms; TR=9,000 ms; TI=2,200 ms; flip angle (FA)=90°; FOV=220×220 mm; matrix=356×351; and voxel size=1.0×1.0×1.0 mm³.

Data analysis
For cortical reconstruction and volumetric segmentation of the whole brain, Freesurfer image analysis suite (version 6.0, http://surfer.nmr.mgh.harvard.edu), which is documented and freely available online, was used. The technical details of these procedures have been described in previous publications. Briefly, the processing stream includes a Talairach transform of each subject’s native brain, removal of the non-
brain tissue, and segmentation of the GM/WM tissue. The cortical surface of each hemisphere was inflated to an average spherical surface to locate both the pial surface and the GM/WM boundary. The entire cortex of each subject was visually inspected, and any topological defects were corrected manually, blind to the subject’s identity. The cortical thickness was computed as the shortest distance between the pial surface and the GM/WM boundary at each point across the cortical mantle. The global mean cortical thickness for each subject was computed by averaging the cortical thickness at each vertex, right and left hemispheres separately, and was used in the statistical analyses. The regional thickness value at each vertex for each subject was mapped to the surface of an average brain template allowing visualization of data across the entire cortical surface (described at http://surfer.nmr.mgh.harvard.edu/fswiki/FsAverage). In addition, the entire cerebral cortex was parcellated into 34 regions, and a variety of surface-based data, including maps of cortical volume and surface area as well as curvature and sulcal depth, were created. Data were resampled for all subjects onto a common spherical coordinate system. The cortical map of each subject was smoothed with a Gaussian kernel of 10-mm full width at half-maximum for the entire cortex analyses. The subcortical volumes were obtained from the automated procedure for volumetric measures of the brain structures implemented in Freesurfer. In all, 27 volumetric measures were investigated and extracted seven subcortical structures (WM, caudate, thalamus, pallidum, putamen, hippocampus, and amygdala) from each hemisphere. WMH volumes were calculated and normalized using an automated localization and segmentation software by NEUROPHET Inc. (Seoul, Korea). For each subject, the calculated WMH volume using FLAIR images was normalized to overall brain volume. The automated WMH segmentation method uses a semi-supervised learning method to segment WMH lesions around the seeds.

**Statistical analysis**

Statistical analyses for demographic data were performed with the Statistical Package for Social Sciences software (SPSS, version 20.0; IBM Corp, Armonk, NY, USA). Assumptions for normality were tested for all continuous variables. Normality was tested using the Kolmogorov–Smirnov test. All variables were normally distributed. The independent t-test and the χ² test were used to assess potential differences between the exercise groups and non-exercise groups for all demographic variables. All statistical analyses had a two-tailed a level of <0.05 for defining statistical significance. The general linear model (GLM) was implemented at each vertex in the whole brain to identify the brain regions in which the Exercise groups showed significant differences in cortical thickness relative to non-exercise group, using the FreeSurfer’s mri_glmfit (described at http://surfer.nmr.mgh.harvard.edu/fswiki/mri_glmfit). All the analyses were performed for the right and left hemispheres separately. For multiple comparisons correction, family-wise error correction p < 0.05 using the Monte Carlo Null-Z simulation with 10,000 permutations was applied. This approach is implemented in FreeSurfer and is based on the AlphaSim algorithm. The seven subcortical structure volumes (i.e., total WM volumes, thalamus, caudate nucleus, putamen, pallidum, hippocampus, and amygdala) were imported into the SPSS 20.0 software for statistical analyses (IBM Corp). To assess the main effects of diagnosis on the volume of subcortical structures, we used analysis of covariance (ANCOVA) with total intracranial volume, education, sex, and age as nuisance variables.

**RESULTS**

Demographic and clinical characteristics of the study participants are summarized in Table 1. There was no significant

| Table 1. Demographic and clinical characteristics of the study participants |
|---------------------------------|-----------------|-----------------|-----------------|
|                                  | Sarcopenia group (N=30) | Control group (N=30) | p value |
| Age (yr)                        | 72.6±5.8          | 73.2±7.1         | NS            |
| Education (yr)                  | 8.1±4.8           | 8.6±5.2          | NS            |
| Sex (M:F)                       | 12:18             | 14:16            | NS            |
| CDR                             | 0                 | 0                |               |
| CERAD-K battery                 |                  |                  |               |
| VF                              | 14.4±3.9          | 14.4±4.1         | NS            |
| BNT                             | 10.9±2.7          | 11.3±2.3         | NS            |
| MMSE                            | 27.9±2.7          | 27.2±2.8         | NS            |
| WLM                             | 16.9±4.3          | 17.2±3.5         | NS            |
| CP                              | 10.2±1.1          | 10.2±1.2         | NS            |
| WLR                             | 5.5±2.2           | 5.3±1.9          | NS            |
| WLRc                            | 8.2±2.2           | 8.9±1.8          | NS            |
| CR                              | 5.3±3.3           | 5.6±2.1          | NS            |
| ASMI (ASM/m²)                   | 5.4±0.6           | 6.0±0.6          | <0.001        |
| Handgrip strength (kg)          | 14.6±4.8          | 22.8±4.4         | <0.001        |
| 5 time-chair stand test (sec)   | 19.5±8.1          | 8.9±2.5          | <0.001        |

Values are presented as mean±standard deviation. NS, not significant; CDR, Clinical Dementia Rating; CERAD-K, the Korean version of Consortium to Establish a Registry for Alzheimer’s Disease; VF, verbal fluency; BNT, 15-item Boston Naming Test; MMSE, Mini-Mental Status Examination; WLM, word list memory; CP, constructional praxis; WLR, word list recall; WLRc, word list recognition; CR, constructional recall; ASMI, appendicular skeletal muscle index; ASM, appendicular skeletal muscle mass
difference in age, education, sex, CDR scores and the CERAD-K scores between the sarcopenia group and the control group. There were significant differences between the groups in the ASMI, handgrip strength, and 5CST results.

When compared with the control group, the sarcopenia group demonstrated significantly reduced cortical thickness in left superior frontal, precentral, right postcentral, inferior parietal, rostral middle frontal, superior parietal, and both lateral occipital and paracentral gyrus (Monte Carlo simulation, p<0.05; Table 2 and Figure 1). However, no significant reductions were observed in the control group compared to the sarcopenia group. In addition, the volumes of total, deep and PV WMH were significantly reduced in the sarcopenia group compared to the control group (p<0.05).

As for subcortical volumes, reduced subcortical volumes were noted in left hippocampus in the sarcopenia group when compared with the control group (Bonferroni corrected p<0.05, Table 3).

In the correlation analysis of the cortical thickness of the

Table 2. Voxel wise group comparison results where a significant cortical thinning was observed in the sarcopenia group relative to the control group (Monte Carlo Z simulation, p<0.05)

| Region                | Cluster size (mm²) | Number of vertex | T max | X    | Y    | Z    |
|-----------------------|-------------------|------------------|-------|------|------|------|
| Left                  |                   |                  |       |      |      |      |
| Precuneus             | 973.3             | 1,876            | 5.50  | -14.7| -58.5| 25.4 |
| Lateral occipital     | 743.3             | 1,030            | 5.28  | -16.8| -87.4| 20.9 |
| Superior frontal      | 518.8             | 1,330            | 4.72  | -12.0| -0.8 | 39.7 |
| Precentral            | 480.1             | 1,127            | 4.64  | -51.4| -4.1 | 7.9  |
| Paracentral           | 224.5             | 578              | 4.73  | -13.3| -32.3| 49.9 |
| Right                 |                   |                  |       |      |      |      |
| Cuneus                | 494.5             | 678              | 5.00  | 6.1  | -83.3| 17.8 |
| Lateral occipital     | 384.4             | 581              | 3.73  | 32.5 | -77.0| 12.3 |
| Postcentral           | 287.5             | 761              | 4.65  | 63.3 | -10.2| 15.6 |
| Superior parietal     | 259.9             | 541              | 4.14  | 16.6 | -60.4| 51.7 |
| Paracentral           | 245.5             | 690              | 4.68  | 14.7 | -23.3| 42.8 |
| Inferior parietal     | 182.9             | 348              | 5.24  | 37.5 | -61.6| 21.3 |
| Rostral middle frontal| 182.6             | 318              | 5.34  | 32.3 | 38.1 | 18.9 |

Table 3. Subcortical and WMHs volumes of the control and the sarcopenia group

| Subcortical volumes (mm³) | Sarcopenia group (N=30) | Control group (N=30) | p value |
|---------------------------|-------------------------|----------------------|---------|
| Left                      |                         |                      |         |
| Caudate                   | 3,120.1±494.1           | 3,115.1±577.5        | NS      |
| Thalamus                  | 5,992.3±895.9           | 6,096.9±577.5        | NS      |
| Pallidum                  | 1,630.5±242.0           | 1,616.8±202.6        | NS      |
| Putamen                   | 4,880.7±792.5           | 4,730.7±537.9        | NS      |
| Hippocampus               | 3,576.3±398.4           | 3,985.3±340.8        | <0.001  |
| Amygdala                  | 1,427.5±270.8           | 1,489.2±189.2        | NS      |
| Right                     |                         |                      |         |
| Caudate                   | 3,117.8±435.4           | 3,109.5±346.7        | NS      |
| Thalamus                  | 6,215.4±558.6           | 6,146.4±574.5        | NS      |
| Pallidum                  | 1,485.6±133.7           | 1,462.2±132.6        | NS      |
| Putamen                   | 4,385.0±564.6           | 4,451.5±523.1        | NS      |
| Hippocampus               | 3,756.4±466.6           | 3,738.2±393.1        | NS      |
| Amygdala                  | 1,533.1±274.0           | 1,583.4±238.9        | NS      |
| WMH volumes (mm³)         |                         |                      |         |
| Total                     | 13.5±10.7               | 5.12±6.2             | <0.01   |
| Periventricular           | 12.6±9.8                | 4.6±5.9              | <0.01   |
| Deep                      | 0.97±1.2                | 0.34±0.4             | <0.01   |

Values are presented as mean±standard deviation. WMH, white matter hyperintensity; NS, not significant.
sarcopenia group with the ASMI, we found a significant positive correlation with the left precuneus (Monte Carlo simulation, p<0.05). There were no significant correlations between MS and the cortical thickness of the sarcopenia group. The 5CST in the sarcopenia group revealed a significant positive correlation with the volumes of PV WMH (p<0.05). In addition, there is no correlations between the cognitive function tests scores and cortical thickness and subcortical volumes in the sarcopenia group.

DISCUSSION

To the best of my knowledge, this is the first study to explore the cortical thinning pattern and the WMH volume reduction in the cognitively normal older adults with sarcopenia, relative to group-matched healthy controls without sarcopenia. In this study, we have found the cortical thinning of the parietal areas including precuneus and superior parietal areas in the sarcopenia group as compared with the control group. The precuneus is thought to be involved in integrating information from multiple sources into additional aspects of spatial and self-representation. In terms of cognitive function, the precuneus, together with the posterior cingulate and prefrontal cortices, has been selectively implicated in episodic memory retrieval-related tasks which is seriously impaired in AD clinical trajectory. Indeed, the precuneus is the hub region of the default mode network (DMN) a subsystem that is presumptively active when a person is left undisturbed to engage in introspective modes of cognition including episodic memory and self-referential and mediating the perspectives of others. A previous study showed aberrant DMN functional connectivity changes in the preclinical AD subjects reflecting a detrimental effect of amyloid retention on functional changes in the course of AD progression. Several previous researches showed cortical volume and thickness reduction in precuneus area especially in early onset AD. A recent study investigated functional and structural neuroimaging changes associated with muscle loss in the patients with Parkinson's disease. They showed core muscle loss in the thigh, associated with DMN degeneration, longer disease duration, and female gender. They suggested identification of risk factors associated with lean muscle mass loss may assist in early prevention of comorbidities such as sarcopenia. Although not specifically indicated the precuneus area, a previous longitudinal study showed that muscle mass is associated with parietal GM volume atrophy, in a middle-aged cognitively normal subjects. Taken these together, our results with precuneus area cortical reduction might be significant aberrant sign of sarcopenia as risk factor of cognitive impairment including AD and other dementia.

In this study, we showed significant reduction of the precentral gyrus in the sarcopenia group compared to the control group. This is in line with the previous structural neuroimaging study with 456 women with frailty. They showed significant volume reductions in the precentral gyrus in the frailty group. They also showed that right supplementary motor area, an area near precentral gyrus was significantly correlated with lower physical activity. In general, the precentral gyrus plays a major role during the execution of a movement or during isokinetic contraction, and therefore is more activated than other brain regions in stronger and fitter individuals. In addition, another previous longitudinal study showed volumes of the primary motor cortex and gait speed. We could not find the associations between 5CSTs and cortical thickness in the sarcopenia group. This might be due to small sample size and difference characteristics between gait speed and 5CSTs. Further structural imaging study with larger samples might be needed to clarify this associations.

We found PV WMH volumes were significantly reduced in the sarcopenia group compared to the control group. In addition, PV WMH volumes were positively correlated with the 5CST test in the sarcopenia group. These results were in accordance with the previous structural neuroimaging studies in the elderly subjects with sarcopenia. A longitudinal study with 104 cognitively normal older adults followed up 13 years showed that increased and progression of PV WMH volumes were associated with decreased gait performance over time, while progression of deep WMH volume was associated with memory decline. Cerebral small vessel disease and its related hypoperfusion is the major cause of WMHs in the brain. In general, WMH is related to vascular risk factors with associated with subsequent stroke mortality, cognitive impairment, gait speed, and functional impairment. Disruption of WM integrity has been considered the pathogenesis of gait impairment in subjects with WMH. Proper gait requires sensory integration, motor planning, and execution of gait; these aspects largely rely on cortical–subcortical neuronal networks. Frontal and temporoparietal cortices correspond with one another to receive and integrate sensory information; these cortices also play a critical role in the execution of gait with subcortical motor structures. Several previous studies reported that PV WM especially in the frontal region contains major subcortical motor tracts with longitudinal WM tracts that subserve gait and balance control. In these regards prevention of small vessel disease with control of vascular risk factors such as hypertension, diabetes, and dyslipidemia might contribute to subsequent prevention of muscle function such as gait speed.
control group. Our result extends results of a prior work by Moon et al., which conducted in AD to subjects with normal cognition. They reported muscle strength was correlated with the left hippocampal volume after adjusting for age and cognitive functions. They suggested shared underlying pathology between sarcopenia and AD though hippocampal atrophy. Current epidemiology studies have suggested that sarcopenia accelerates cognitive impairment, and this cognitive change has been reported to be related to poor muscle-brain axis mediated by an imbalance in myokine secretion. Subsequently, the imbalanced secretion of myokines leads to memory impairment by upregulation of proinflammatory cytokine production through the blood brain barrier crossing. Several previous studies reported that exercise may induce secretion of myokines, including irisin, brain-derived neurotrophic factor (BDNF), and cathepsin B in skeletal muscle, and ultimately contributes to the improvement and maintenance of memory function. In these regards, muscle function and mass improvement by appropriate physical exercise may contribute to hippocampal volume increase related with memory function.

There are several limitations that must be taken into consideration. First, subjects were recruited from a single center, which limits generalizability of results. Second, our study design was cross sectional and sample sizes were small. Third, homogeneity of our study participants makes the results difficult to generalize. Indeed, even in cognitively normal older adults, there might be potential underlying pathologies such as cerebral beta amyloid accumulation. In conclusion, we observed cortical thickness reductions and WMH changes in sarcopenia. In addition, we found significant correlations between cortical thickness/WMH volumes and muscle function and strength in sarcopenia. These structural changes might explain the neurobiological mechanisms associated with sarcopenia, but longitudinal studies will be needed to identify the mechanisms of these structural changes.

 Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Se-Hong Kim, Youngmi Eun, Hyun Jung Kim. Data curation: Se-Hong Kim, Youngmi Eun. Formal analysis: Youngmi Eun, Ju-Hye Chung. Funding acquisition: Hyun Jung Kim, Ju-Hye Chung, Se-Hong Kim. Investigation: Ju-Hye Chung. Methodology: Ju-Hye Chung, Hyun Jung Kim. Project administration: Hyun Jung Kim, Se-Hong Kim. Resources: Hyun Jung Kim, Se-Hong Kim. Software: Ju-Hye Chung. Supervision: Se-Hong Kim. Validation: Ju-Hye Chung. Visualization: Ju-Hye Chung. Writing—original draft: all authors. Writing—review & editing: Ju-Hye Chung, Hyun Jung Kim, Se-Hong Kim.

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