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Computed tomography-based skeletal muscle and adipose tissue attenuation: variations by age, sex, and muscle

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Abstract

Objective: This study aimed to investigate how skeletal muscle attenuation and adipose tissue (AT) attenuation of the quadriceps, hamstrings, paraspinal muscle groups and the psoas muscle vary according to the targeted muscles, sex, and age.

Design: Population-based cross-sectional study.

Setting: Community-dwelling old population in Reykjavik, Iceland.

Subjects: A total of 5331 older adults (42.8% women), aged 66–96 years from the Age, Gene/Environment Susceptibility (AGES)- Reykjavik Study, who participated in the baseline visit (between 2002 and 2006) and had valid thigh and abdominal computed tomography (CT) scans were studied.

Methods: Muscle attenuation and AT attenuation of the quadriceps, hamstrings, paraspinal muscle groups and the psoas muscle were determined using CT. Linear mixed model analysis of

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Author Contributions:
All authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; participated in drafting the article or revising it critically for important intellectual content; and gave final approval of the version to be submitted.

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variance was performed for each sex, with skeletal muscle or AT attenuation as the dependent variable.

Results: Muscle attenuation decreased, and AT attenuation increased with age in both sexes, and these differences were specific for each muscle, although not in all age groups. Age-related differences in muscle and AT attenuation varied with specific muscle. In general, for both sexes, skeletal muscle attenuation of the hamstrings declined more than average with age. Men and women displayed a different pattern in the age differences in AT attenuation for each muscle.

Conclusions: Our data support the hypotheses that skeletal muscle attenuation decreases, and AT attenuation increases with ageing. In addition, our data add new evidence, supporting that age-related differences in skeletal muscle and AT attenuation vary between muscles.

1. Introduction

Changes in skeletal muscle (SM) quantity and quality are widely recognized and particularly relevant, owing to their significant impact on functional impairments and disability associated with aging. Thigh muscles have major action in locomotion, are associated with mobility performance (particularly during aging) [1, 2], and have greater responsiveness to age-related change or therapeutic intervention compared with the whole body [3]. The psoas muscle, which supports the movement of the hip joint, has been used as a reliable indicator of sarcopenia and a surrogate marker for frailty, being simple and convenient to measure [4]. Trunk muscles are also essential for activities of daily living, assisting on balance control [5]. In particular, the muscles that support the spine (paraspinal muscles) are receiving revived attention due to the link with spinal degeneration and low back pain [2, 6]. These two conditions are more commonly in older adults.

Computed tomography (CT) has been used extensively to characterize both the size and composition of SM [7]. SM attenuation on CT scan imaging has been considered a marker of muscle fat infiltration [8]. Overall, it is expected that fat infiltration of the muscle increases with advancing age [9]. Although, the relevance of SM attenuation has been increasingly recognized, being correlated with several health outcomes [10–12], including mortality risk [13], how attenuation changes during aging and across different muscles is poorly described. Many of the previous studies addressing this topic had limitations, including comparisons between two age groups (adults vs. older adults) with a small number of subjects per group [14–16]. Recently, two studies assessed the age-related differences in trunk muscle size and density with larger sample sizes but exploring wide age-range groups (one or two age decades) [17, 18].

Moreover, different adipose depots can be separately quantified using CT, such as visceral, subcutaneous, pericardial, intermuscular, and intramuscular, while only the last two compartments can be found in the skeletal muscle. However, studies have mostly focused on the visceral and subcutaneous adipose tissue (AT) compartments and the associations between their accumulation and metabolic outcomes [19–21].

To date, the clinical implications of the radiographic characteristics of SM and AT are currently under debate [22, 23], and little is known about the age-related changes in muscle density, and how it varies with sex and between specific muscles. Moreover, no study has assessed age-related differences in trunk and thigh AT attenuation.

This study aimed to examine how SM and AT attenuation of the quadriceps, hamstrings, paraspinal muscle groups and the psoas muscle vary according to the targeted muscles, sex, and age. We hypothesized that SM attenuation would decrease with age and AT attenuation would increase, and that the age-related differences in both measures vary between different muscles with specific mechanical functions. Also, we expect that women would have lower mean attenuation values than men.

2. Material and Methods

2.1 Study design and population

The study cohort consisted of older adults from the AGES-Reykjavik Study, a single-center prospective population study of Icelandic men and women. Design and recruitment have been described in detail [24]. From the 5764 men and women (aged 66 to 96 years) who participated in the baseline visit (between 2002 and 2006), 5331 individuals with complete thigh and abdominal CT scans (42.8 % male) were included in the present study.

All participants provided written informed consent, and the study was approved by the Icelandic National Bioethics Committee (VSN: 00-063) and the Institutional Review Board of the Intramural Research Program of the National Institute of Aging.

2.2 Measures

CT measurements in the mid-thigh and abdomen (at the L4/L5 vertebrae) were performed using a 4-detector CT system (Sensation 4, Siemens Medical Systems, Erlangen, Germany), using a single 10-mm-thick transaxial section, as previously described [25, 26]. For each muscle, SM attenuation was computed by measuring the mean attenuation value from all pixels within the range of 0 to 100 HU. Lower HU indicates greater fat infiltration [8]. The intramuscular AT (defined as AT infiltrated within a single muscle or muscle group) attenuation of each muscle was determined by measuring the mean attenuation value from all pixels with HU between −190 and −30. Further details on methodology are described in Appendix 1.

We considered several potential confounders: body mass index (BMI), education, physical activity, self-reported health status, smoking status, health conditions or diseases score, alcohol consumption, High-sensitive C-Reactive Protein (hs-CRP), muscle area, and intramuscular AT area. The full description of the covariates is provided in Appendix 1.

2.3 Statistical analysis

Mean and standard-deviation (SD) or percentages for categorical variables were used to summarize subject characteristics. Differences in the distributions of baseline characteristics between men and women were assessed using 2-sided t tests for continuous variables and χ^2 test for categorical variables. We found strong indication of differences between men and women in the relationships between age and outcomes of interest. Therefore, all analyses were conducted separately for men and women. For each muscle, repeated measures

ANOVA with Tukey's post hoc test were applied to examine differences in the unadjusted attenuation values of SM and AT by age group.

Linear mixed model analysis of variance was performed for each sex, with SM or adipose tissue attenuation (in HU) as the dependent variable. For the model selection process, we used a top-down strategy. [27] A full model was fit, and an unstructured covariance matrix used for the random effects. Afterwards the model was reduce using the F-statistics, the final model was performed using REML estimation. The random effects models accounted for between-subject variation and adjusted for within-subject correlations between repeated measurements. Thus, each participant had a subject-specific intercept. The fixed effects structure was the same for both sexes (i.e., all significant variables in each model were kept for both models). The fixed effects in the models included the muscle, age group and interaction term (muscle x age group), and the examined covariates. To examine differences in attenuation between age groups, multiple comparisons were performed and adjusted using Bonferroni method. Finally, to compare age differences in SM and AT attenuation between muscles, linear contrasts were constructed to compare the age difference for each muscle with the mean age difference among all muscles.

Except for age that had no missing data, the proportion of missing data in the cohort was extremely low (Appendix 1). However, for each participant, all the available data was used, because cases met the missing-at-random criteria.

Significance testing was two-sided and based on a 5% probability level. The package lme4 [28], nlme [29], and lsmeans [30] in the software r [31] were used for the analysis.

3. Results

The study population consisted of 5331 older adults aged 66-99 years (average age 76.5 years), 57.2% were women, and mean BMI was in the overweight range. Men and women were similarly distributed by age groups, except for the younger age group that had more women than men (11.2% vs. 8.5%, respectively). Except for age, demographic and clinical measures differed significantly between men and women, and men had, in general, better clinical and behaviour characteristics (except for alcohol and smoking behaviors) than women (Appendix 2). Similar patterns were present when men and women were stratified by the following age groups: 66-69 years, 70-74 years, 75-79 years, 80-84 years, and 85-96 years (Appendix 3).

Table 1 presents the attenuation values of SM and AT across all muscles, by sex and age group. Pooled muscle attenuation measurements from all muscles in men averaged 40.5 ± 6.8 HU and were significantly higher than in women (37.4 ± 7.7 HU; $P<0.001$). For both, men and women, muscle attenuation differed among all muscles ($P<0.001$) and was progressively lower as the age group increased ($P<0.001$). Pooled AT attenuation across all muscles in men averaged −68.7 ± 10.1 HU was significantly higher (i.e., less negative) than in women (−70.9 ± 11.4 HU; $P<0.001$). In contrast to SM attenuation, variation in AT attenuation was not consistently different across all age groups. Also, except for the psoas muscle, men had higher AT attenuation values (i.e., less negative) than women for all muscles (P<0.001; Table 1).

Figure 1 displays the variation in SM and AT attenuation by muscle within each age-sex group. Overall, in both sexes, muscle attenuation decreased with age for all muscles, although, a different pattern of change with age and by muscles was observed. For example, in men and women, the two older age groups (bottom bars) had consistently lower muscle attenuation across all examined muscles, compared with the two younger age groups (top bars). In men, the hamstrings had significantly different muscle attenuation across all age groups. In women, the two younger age groups (66-69 years and 70-74 years) had similar muscle attenuation at the quadriceps, hamstrings, and psoas.

Overall, AT attenuation increased (i.e., less negative) with age for all muscles, but these changes were less consistent than for SM. For example, in men, a unique pattern was observed in the quadriceps and hamstrings muscles, as both displayed similar AT attenuation values across all age groups. In women, the oldest age group (85+ years) had significantly higher AT attenuation (i.e., less negative) than women in the age groups 66-69 and 70-74 years old, across all examined muscles.

We found that age differences between muscles in SM and AT attenuation varied by sex (Figure 2). In general, for both sexes, skeletal muscle attenuation of the hamstrings declined more than average with age. Of note, we found that only in men the difference with age for paraspinal muscle attenuation was smaller than the other muscles, thus declined less than average with age. Also, differences in AT attenuation in each of the measured muscles between age groups showed a different pattern in men compared with women. In men, the psoas AT attenuation increased more than the average, while the opposite was observed in the quadriceps. However, both quadriceps and hamstrings showed a stable age difference across the age groups, in line with the similar mean AT attenuation values observed in Figure 1. In women, changes in AT attenuation increased with age across all muscles. Specifically, the difference in psoas AT attenuation from the youngest category of age compared with the first age groups was significantly higher from the pooled mean age difference of all other muscles, while values were similar on the highest two ages groups.

4. Discussion

In this cross-sectional study we found that overall, SM attenuation decreases, and AT attenuation increases with age in both sexes, and these changes are muscle-specific. Despite this trend, similar attenuation values (particularly for AT) were observed in different age groups. This evidence implies that, although age is a significant predictor of muscle and AT quality, differences are more likely among extreme age-groups. Finally, we found different patterns of change in muscle and AT attenuation with age and sex among individual muscles or muscle groups, adding evidence that aging leads to distinctive adaptations in these two linked tissues, and highlight the need to consider sex as covariate.

We found that SM attenuation of different muscles decreases during ageing. Potential mechanisms that may explain the lipid accumulation in the muscle include imbalance between fatty acid uptake, oversupply of plasmatic fatty acids, and oxidation and myocell adipogenic differentiation cells differentiating into adipogenic cells [32, 33]. Although age-related declines in muscle strength and size are well-described [34], limited data exists on how muscle attenuation changes in a cohort of older adults [17]. Our results are consistent with those from a prior study showing that muscle density (in all ten trunk muscles) was negatively associated with age in people aged 40 to 90 years [17]. Anderson et al. [15] previously reported that trunk muscles attenuation was lower in older adults than in younger adults. In older adults aged 70-79 years, a study reported a decrease in mid-thigh SM attenuation as a function of increasing age [10]. Our data add to these previous studies as we included a cohort of older adults aged 66 to 96 years (stratified in 5 age groups) and demonstrated that SM attenuation did not differed between all age groups, and that age-group differences varied between specific muscles. Lower SM attenuation is related to greater fat infiltration (lipid content) [8], which can lead to muscle force reduction [10, 35]. However, muscle force is dependent on other structural factors, such as changes in fiber pennation angle and connective tissue properties (aponeurosis stiffness)[35]; this may explain why muscle strength progressively decreases during ageing, even in the absence of significant changes in SM attenuation. Moreover, lower density of lumbar muscles has been related to increased low back pain, decreased lumbar lordosis, increased postural sway, and poor physical function [2, 36, 37].

We also found that AT attenuation displayed a trend to increase with age, which was also muscle- and sex-dependent. However, compared with SM attenuation these age-related changes were less consistent. Two previous studies reported that older adults (aged ~70 years old) had significantly higher intramuscular AT percentages in the muscle groups of the thigh compared with young adults (age <30 years) [14, 16]. However, data collected from population-based cohorts found no evidence of association between AT area and age [10, 38]. The comparison between our data and those previous studies are limited by differences in subjects' age and AT assessment. Thus, some have used MRI-derived AT content (in %) [14, 16], while other used AT area (cm^2) measured by peripheral-CT [38] or CT [10].

Few studies have provided insights into the meaning of this radiographic characteristic, and the results are expected to differ depending on the imaging modality, scan location, and AT site/compartment. Each AT measure may represent different risk factors to metabolic and muscle health, particularly in older adults. In general, higher AT attenuation has been associated with negative health outcomes [39, 40]. However, some findings from abdominal and mid-thigh AT attenuation are less consistent, as limited associations with mobility limitations and poor performance were reported [41]. The reason for these divergent associations is still unclear, and the potential mechanisms that underlie the CT attenuation of AT clinical and biological relationships have rarely been explored. Recently, it was revealed that intermuscular AT may act in a similar manner to visceral AT to promote insulin resistance, and that factors secreted from intermuscular AT contributed to the development of insulin resistance [23]. Also, findings suggest that due to its close proximity, secreted free fatty acids, proteins, and cytokines from intermuscular AT could have a strong influence on regulating muscle insulin sensitivity and metabolic function [23].

In the current study we also demonstrated that SM attenuation in all four studied muscles was significantly lower in women than in men. This finding is in agreement with studies reporting CT muscle attenuation for trunk muscles [15, 17], thigh muscles [10], and paraspinal [12].

Regarding AT attenuation, we found that values were higher (i.e., less negative) in men than women for all muscles, except for the psoas muscle. No comparisons with other studies are possible, as this is the first study reporting the AT attenuation found within each individual muscle.

Our data supported that age-related changes in the attenuation of SM and AT are muscle-dependent. Similarly, age-related declines in muscle attenuation were also reported to vary significantly between trunk muscles [15, 17]. These findings are somewhat supported by two MRI-based studies reporting that the intramuscular AT content changes during aging varied between muscles [14, 16]. Finally, we also found that the age differences in AT attenuation varied according to the sex and muscle, which did not mimic the changes observed in the SM. The reasons for these differences in AT attenuation between muscles are also unclear. Our findings support the need of developing preventive and therapeutic approaches to target specific muscles more affected by aging. Regular physical activity, resistance exercise training and multicomponent exercises (including muscle power training) may be promising interventions based on the positive results in reducing intramuscular fat accumulation in older adults [42–44]. The strengths of our study are the analysis of the two tissues' attenuation values and four different muscles, the large sample size, data stratification into 5-year age groups, and the statistical models' adjustment for lifestyle, medical history, and several other factors.

However, findings should be interpreted in light of the study limitations: data is cross-sectional, the age groups '66 to 69 years' and '85 to 96 years' represent only ~9% of the total sample, and is based on a single Icelandic community. Finally, comparisons between different studies should be interpreted with caution due to the lack of consistent image acquisition and analysis protocols (including criteria for the upper and lower HU cut-offs used to characterize SM and AT attenuations, and nomenclature).

In conclusion, our data support the hypotheses that SM attenuation decreases, and AT attenuation increases through ageing, that in general, attenuation values are lower in women than in men and variable between muscles, and that age-related differences in both measures vary between muscles. This study adds novel insight into the muscle impairment due to structural age-related changes in SM and the AT specific by muscle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

Overall, skeletal muscle attenuation decreases, and adipose tissue (AT) attenuation increases during ageing.

Muscle and AT attenuation followed a distinctive pattern of change depending on the age group. Muscle and AT attenuation are dependent on sex and muscle group.

The hamstrings muscle attenuation declined more than average with age.

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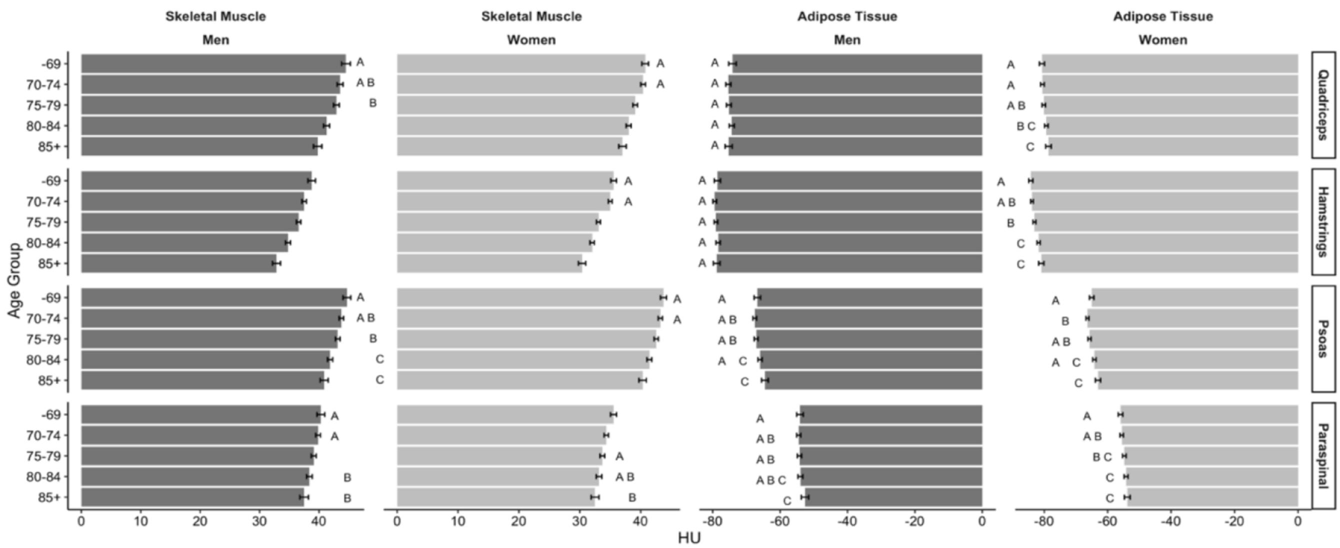

Figure 1.

Mean ± SE of skeletal muscle attenuation and AT attenuation by muscle (Quadriceps, Hamstrings, Psoas, and Paraspinal), sex and age group. Within each muscle-sex group, age groups marked by the same letter (A, B, C) are similar from each other ($P > 0.05$).

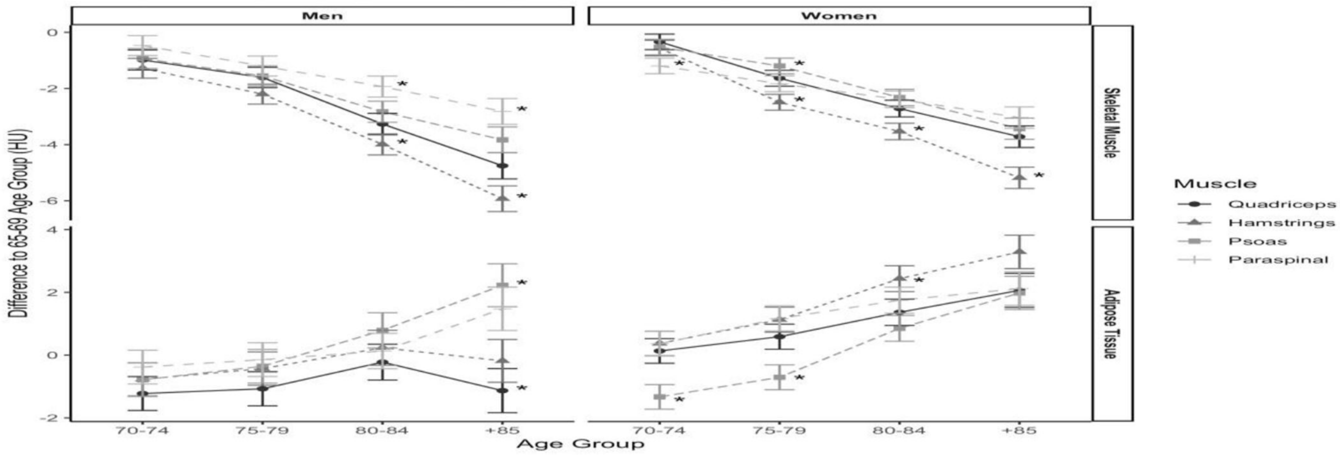

Figure 2.

Differences in skeletal muscle and AT attenuation between the youngest category of age (66-69) and each one of the others (70-74, 75-79, 80-84, +85) by muscle (circle = Quadriceps; triangle = Hamstrings; square = Psoas; cross = Paraspinal). Age difference for muscle is significantly different than pooled mean age difference of all other muscles (* $P < 0.05$).

Table 1.

Skeletal muscle and AT attenuation for each muscle stratified by age group and sex.

	Men - Age group (years)					Women - Age group (years)				
	66-69, n=193	70-74, n=688	75-79, n=693	80-84, n=511	85-96, n=196	66-69, n=343	70-74, n=898	75-79, n=850	80-84, n=706	85-96, n=253
Skeletal Muscle attenuation, HU										
Quadriceps	48.0 (4.0)	47.1 (4.4)	46.2 (4.3)	44.3 (4.7)	42.8 (4.5)	44.9 (4.0)	44.3 (4.1)	42.7 (4.4)	41.6 (4.3)	40.5 (4.4)
Hamstrings	39.8 (5.9)	38.6 (6.0)	37.4 (5.9)	35.5 (6.4)	33.1 (6.3)	36.3 (6.0)	35.6 (5.8)	33.6 (6.2)	32.6 (6.0)	30.8 (6.3)
Psoas	45.6 (3.9)	44.7 (3.9)	44.1 (3.7)	42.8 (4.1)	41.6 (3.9)	44.7 (3.5)	44.0 (3.2)	43.2 (3.3)	42.0 (3.6)	40.9 (3.4)
Paraspinal	37.3 (5.2)	36.4 (5.2)	35.2 (5.0)	34.0 (5.40	32.2 (4.8)	32.4 (5.1)	30.7 (5.4)	29.4 (5.3)	28.1 (5.4)	26.7 (4.9)
Adipose tissue attenuation, HU										
Quadriceps	−73.4 (7.8)	−74.7 (8.3)	−74.2 (8.1)	−72.9 (8.2)	−73.9 (7.7)	−80.0 (7.4)	−79.9 (7.3)	−79.2 (7.1)	−77.9 (7.2)	−76.6 (7.0)
Hamstrings	−77.0 (6.6)	−77.6 (6.8)	−77.1 (6.7)	−76.2 (6.9)	−76.5 (7.0)	−82.6 (5.7)	−82.2 (5.5)	−81.3 (5.9)	−79.6 (6.3)	−78.2 (6.6)
Psoas	−64.8 (7.6)	−65.5 (7.4)	−64.9 (7.3)	−63.4 (7.5)	−61.7 (7.2)	−62.2 (7.3)	−63.6 (7.4)	−62.6 (7.5)	−60.8 (7.3)	−59.4 (7.2)
Paraspinal	−59.1 (5.5)	−60.2 (6.2)	−59.6 (6.3)	−59.4 (6.4)	−58.9 (6.2)	−61.7 (5.7)	−62.0 (5.8)	−61.4 (5.7)	−60.6 (6.0)	−60.3 (6.0)

Note: Values are unadjusted mean (SD)