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Effect of Exercise Modality during Weight Loss on Changes in Muscle and Bone Quality in Older Adults with Obesity

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Abstract

Background: Little is known about the effect of exercise modality during a dietary weight loss program on muscle size and quality, as measured by computed tomography (CT). Even less is known about how CT-derived changes in muscle track with changes in volumetric bone mineral density (vBMD) and bone strength.

Methods: Older adults (66±5 years, 64% women) were randomized to 18-months of diet-induced weight loss (WL), WL with aerobic training (WL+AT), or WL with resistance training (WL+RT). CT-derived muscle area, radio-attenuation and intermuscular fat percentage at the trunk and mid-thigh were determined at baseline (n=55) and 18-month follow-up (n=22–34), and changes were adjusted for sex, baseline value, and weight lost. Lumbar spine and hip vBMD and finite element-derived bone strength were also measured.

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Results: After adjustment for the weight lost, muscle area losses at the trunk were −7.82 cm^2 [−12.30, −3.35] for WL, −7.72 cm^2 [−11.36, −4.07] for WL+AT, and −5.14 cm^2 [−8.65, −1.63] for WL+RT (p<0.001 for group differences). At the mid-thigh, decreases were −6.20 cm^2 [−10.39, −2.02] for WL, −7.84 cm^2 [−11.19, −4.48]) for WL+AT, and −0.60 cm^2 [−4.14, 2.94] for WL+RT; this difference between WL+AT and WL+RT was significant in post-hoc testing (p=0.01). Change in trunk muscle radio-attenuation was positively associated with change in lumbar bone strength (r=0.41, p=0.04).

Conclusions: WL+RT better preserved muscle area and improved muscle quality more consistently than WL+AT or WL alone. More research is needed to characterize the associations between muscle and bone quality in older adults undertaking weight loss interventions.

Keywords

randomized controlled clinical trial; finite element bone strength; sarcopenia; bone density; exercise modality

1. INTRODUCTION

By 2040 there will be about 82.3 million Americans aged 65 and older,[1] and at least a third of them are projected to live with obesity.[2] Primary lifestyle interventions to manage obesity include caloric restriction and exercise, which are known to induce weight loss,[3] improve mobility,[4] and reduce cardiovascular disease risk.[5] Concomitant muscle and bone loss, however, along with the potential to exacerbate age-related risk of sarcopenia and osteoporosis, has stalled widespread clinical weight loss recommendation for this demographic.[6–8]

Evidence from randomized controlled weight loss trials conducted in older adults suggests that concurrent resistance training may modestly prevent loss of muscle and bone mass,[9–11] usually measured by dual energy x-ray absorptiometry (DXA). However, DXA alone does not capture all properties of muscle and bone that contribute to their strength.[12] Computed tomography (CT) is increasingly used to complement DXA imaging in clinical studies because it provides high-resolution 3D measures of morphological muscle quality ("fatty infiltration" or inter- and intramuscular fat deposition) and bone density and strength. For instance, increased intermuscular and intramuscular fat deposition (indicative of poorer muscle quality), measured in CT, has been associated with mobility limitations,[13] lower muscle strength independent of muscle mass,[14] increased fracture risk,[15] increased likelihood of incident falls,[16] and mortality.[17] Furthermore, lifestyle interventions, such as nutritional supplementation and physical activity, have been shown to influence positively the muscle composition of older adults with mobility limitation.[18] Despite evidence supporting its use as a biomarker, studies examining the effect of exercise type on CT-derived muscle quality measures in older adults undergoing diet-induced weight loss is currently lacking.

In addition to muscle quality metrics, CT also provides information about bone quality. CT-derived bone metrics like volumetric bone mineral density (vBMD) and bone strength estimated through finite element (FE) modeling have been successfully used for fracture-risk assessment.[19] Previous studies suggest that muscle mass is associated with bone health in older adults.[20,21] In addition to muscle mass, higher calf muscle density (indirect measure of inter- and intra-muscular fat) has been associated with better bone health cross-sectionally[16] and paraspinal muscle fat fraction has been associated with lower lumbar vBMD,[22] but it has not been examined directly whether changes in muscle quality are associated with changes in bone strength, nor whether these local bone-muscle health associations track longitudinally or apply to other regions such as the hip. If muscle quality were an additional contributor to bone strength in older adults, then interventions that improve or preserve muscle quality might also be preferentially indicated for bone health. Indeed, data from an epidemiological study in older men shows that appendicular lean mass is associated with bone CT parameters independently of muscle strength and power,[23] highlighting the influence of other muscle properties. Muscle and bone are not only coupled via mechanotransduction, which stretches collagen fibers and periosteum at the muscle-bone interface; their mechanical and endocrine interaction also involves pleiotropic genes and secretory factors, such as IGF-1, myostatin, osteocalcin, irisin, osteopontin, sclerostin, and others.[24–27]

Leveraging the platform provided by the Cooperative Lifestyle Intervention Program-II (CLIP-II; NCT01547182) randomized controlled trial (RCT), for which treatment effects on DXA-derived body composition and CT-derived vBMD and bone strength outcomes have been published,[11,28–30] the primary purpose of this exploratory analysis is to characterize the effect of a dietary weight loss program alone, with aerobic training, or with resistance training on CT-derived trunk and mid-thigh cross-sectional skeletal muscle area (CSA), muscle radio-attenuation, intermuscular fat deposition, and skeletal muscle index (SMI_{CT}: CSA/[patient height]^2). The secondary purpose is to examine how changes in CT-derived muscle area and muscle radio-attenuation associate to changes in CT-derived bone metrics (vBMD and finite element-derived bone strength).

2. METHODS

2.1 Study Sample

Details of the CLIP-II design and its methods are published,[31] as well as the primary outcome paper that includes the full trial inclusion/exclusion criteria and CONSORT diagram.[32] Briefly, CLIP-II was an 18-month RCT that included 249 older adults (66.8±4.7 years) with obesity (33.8±3.6 kg/m^2), cardiovascular disease (CVD; 26.1%) and/or metabolic syndrome (84.3%), and self-reported mobility disability (self-reported difficulty with walking ¼ mile), with dual primary outcomes of mobility (400-m walk time) and muscle strength (knee extensor strength). Participants were randomized to diet-induced weight loss only (WL), weight loss plus aerobic training (WL+AT) or weight loss plus resistance training (WL+RT) in a community-based setting, with the goal of eliciting 7–10% body mass loss. The caloric deficit was ~330 kcals/day during the intensive phase (months 1–6), followed by a transition phase (months 7–12), and maintenance phase (months 13–18). The caloric deficit aims of the transition phase depended on the progress of the individual, but during this phase the focus moved gradually towards weight maintenance for the last six months, with emphasis on portion control and improving the quality of food choices. WL+AT consisted of walking for 45-minutes/day with an intensity of 12–14 on the Borg Rating of Perceived Exertion Scale four days/week, and WL+RT involved upper and lower body machine-based exercise performed for 45-minutes/day with 3 sets of 10–12 repetitions at 75% of 1 repetition maximum four days/week with progressive overload. As reported in the main outcome paper, WL plus exercise groups improved 400 meter walk time (~17 second reduction) and knee extensor strength normalized by body mass (~15% improvement) as compared to WL alone, with no difference between AT or RT groups.[32]

This present analysis focuses on a subset of these participants that belong to the last two recruitment phases (waves 7 and 8) who consented to receive a thigh and a lumbar CT scan at baseline (n=55) and 18-month follow-up (n=34). Helical CT scans of the abdominal trunk and both thighs were acquired on a 64-slice scanner (LightSpeed VCT, General Electric Medical Systems, Milwaukee, WI) at 120 kVp and 250 mA, with a slice thickness of 2.5mm for the trunk and 0.625mm for the thighs. Sample sizes for the CT-derived muscle and bone outcomes are reported in eFigure 1. The larger CLIP-II study population and the CT subset were very similar with regard to age (66.8 ± 4.7 vs 65.8 ± 4.3 years), sex (71.1% vs 63.6% female), race (32.1% vs. 27% Black), and body mass index (BMI; 33.8 ± 3.6 vs 34.0 ± 3.5 kg/m^2).[32] All participants provided written informed consent prior to enrollment (IRB00018631).

2.2 CT-acquired Muscle Measures

A single CT slice was selected from the abdominal trunk at the middle of the third lumbar vertebral level (L3; half of the vertebral body height)[33] and another single CT slice from the mid-thigh. The mid-thigh was defined as equidistant between the lesser trochanter and the intercondylar fossa,[34] using the right femur as measurement reference on the CT scouts for placement consistency. The selected CT slices were analyzed by a blinded, trained investigator using Mimics (v.23; Materialise, Leuven, Belgium). The abdominal trunk and the mid-thigh are both body regions widely used in sarcopenia and exercise research and are clinically relevant in the assessment of bone health.[35,36] Mid-thigh data is reported as the average of both legs, and trunk data is reported bilaterally.

For each body region, skeletal muscle tissue was segmented by thresholding within the range of −29 to 150 Hounsfield Units (HU) and intermuscular fat between −190 to −30 HU.[37] Thresholding operations were followed by manual tracing to exclude visceral content, skin, and bone. Adipose tissue depots located between muscle fiber bundles and within the deep fascial boundary of whole muscle surfaces were segmented as intermuscular fat areas.[38] The intermuscular fat percentage was calculated by dividing the intermuscular adipose tissue area by the sum of the total muscle area and the intermuscular adipose tissue area. Figure 1 shows example segmentations of female participants with the same BMI but contrasting muscle areas and intermuscular fat percentages. Muscle radio-attenuation, which indirectly quantifies lipid droplets within muscle fibers, was measured as the average HU from the muscle area.

A random sample of 10% (n=6) of the baseline study cohort was analyzed thrice by the same investigator, and the coefficient of variation was <2% for muscle measures and <6% for fat measures. Inter-reader intra-class correlation coefficients for CT-derived muscle measurements collected by our group range from 0.94 to 0.99, indicating excellent reliability.[39]

2.3 CT Skeletal Muscle Index of Sarcopenia

The SMI_{CT} (cm^2/m^2) was obtained by normalizing trunk muscle area by each participant's height squared.[40,41] SMI_{CT} cut-offs for sarcopenia used were 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men.[41]

2.4 CT-acquired Bone Measures

The methods for the measurement of vBMD and of the finite element modeling-derived bone strength have been previously described for this cohort.[11,29,30] To explore muscle-bone associations, the following bone outcomes were used: mean integral vBMD of the L1–L4 vertebrae, mean integral vBMD of the total hip (left and right average), compressive strength averaged for the L1–L4 vertebrae, and hip strength in a configuration simulating impact from a sideways fall[30,42] (referred to here as "fall strength"; left and right average). Bone strength is a function of geometry, cortical thickness, and vBMD[30] and the higher the strength in a particular configuration, the higher the resistance to fracture in that configuration.

2.5 Statistical Analysis

Baseline characteristics were summarized as means and standard deviations (mean ± SD) for continuous variables or counts and percentages [n (%)] for discrete variables. Data was analyzed using SAS (v.9.4. SAS Institute Inc., Cary, NC) and all statistical testing was two-sided and based on a 5% probability level. The 18-month changes were calculated by subtracting the baseline values from follow-up values; therefore, a negative mean change denotes a decrease from baseline to follow-up. As assumptions of independence, homogeneity of variance, and normality of experimental errors were confirmed, intervention effects on CT-derived muscle measures were estimated using a general linear model fit with treatment group, sex, and wave, adjusted for baseline value of each muscle outcome (Model 1). To generate Model 2, Model 1 was further adjusted for weight change over 18 months. Pairwise Tukey tests were used when the generalized linear model F-test indicated the presence of linear contrast among the means. Associations of the CT-derived muscle measures with vBMD and bone strength were estimated by partial Pearson correlation coefficients (r) adjusted for sex, recruitment wave, and baseline value of the bone variable.

3. RESULTS

3.1 Participant Characteristics

Baseline age, sex, race, body mass, and BMI for the 55 subgroup participants are reported in Table 1. The 34 participants with 18-month follow-up CT data were demographically similar to the baseline sample and the characteristics remained balanced among randomization groups (eTable 1). In accordance with the goals of the trial, all three treatment groups lost significant weight. Total body mass changes adjusted for baseline body mass were mean [95% CI]: −6.14 kg [−11.76, −0.52] for WL alone; −11.74 kg [−16.24, −7.23] for WL+AT; and −9.05 kg [−14.01, −4.08] for WL+RT; no difference between groups was found (p=0.13). Expressed as a percentage of baseline body weight, the difference between WL and WL+AT was −6.2% [−15.4, 2.9], between WL and WL+RT was −4.2% [−13.5, 5.1], and between WL+AT and WL+RT the difference was 2.0% [−6.4, 10.5]; no difference between groups was found (p=0.35).

3.2 Intervention Effects on CT Muscle Measures

Intervention effects on muscle measures are shown in Table 2. At the trunk, WL+RT lost mean [95% CI]: −4.97 cm^2 [−9.30, −0.63] of muscle CSA, while WL+AT lost −8.14 cm^2 [−12.64, −3.63] and WL lost −5.24 cm^2 [−10.54, 0.04]). At the mid-thigh WL+RT experienced a loss of −0.57 cm^2 [−5.10, 3.96] while WL+AT lost −8.85 cm^2 [−13.11, −4.60] and WL lost −3.94 cm^2 [−9.12, 1.25]); this difference between WL+AT and WL+RT was significant in post-hoc testing (p=0.01). Following adjustment for weight lost, muscle area losses remained attenuated in WL+RT (−5.14 [−8.65, −1.63] at trunk; −0.60 [−4.14, 2.94] at mid-thigh), while both WL and WL+AT experienced similar muscle area losses at the trunk (WL: −7.82 cm^2 [−12.30, −3.35]; WL+AT: −7.72 cm^2 [−11.36, −4.07]), and mid-thigh (WL: −6.20 cm^2 [−10.39, −2.02]; WL+AT: −7.84 cm^2 [−11.19, −4.48]). Both WL+RT and WL+AT tended to increase trunk muscle radio-attenuation, while WL alone tended to decrease it (p=0.01 for between-group comparisons in the weight loss-adjusted model), although post hoc testing did not reveal pairwise differences (eTable 2). When expressed as a percentage of the muscle area and adjusted for weight lost, the reductions in intermuscular fat percentage of WL+RT were comparable to those of WL+AT at the trunk (WL+RT: −1.24% [−2.34, −0.14]; WL+AT: −1.31% [−2.36, −0.25]), and were higher than those experienced by both WL alone and WL+AT at the mid-thigh (WL+RT: −2.59% [−3.71, −1.47]; WL: −2.07% [−3.44, −0.70]; WL+AT: −2.07% [−3.13, −1.01]; p<0.01 between group, no pairwise differences in post hoc testing). The ratio of muscle area to fat area lost at the trunk is 3.2:1 for WL, 2.7:1 for WL+AT, and 2.0:1 for WL+RT. The ratio of muscle to fat area losses at the mid-thigh are 1.6:1 for WL, 1.9:1 for WL+AT, and 0.2:1 for WL+RT.

3.3 Intervention Effects on CT Skeletal Muscle Index of Sarcopenia

At baseline, average SMI_{CT} was 45.6 ± 6.9 cm^2/m^2 for women and 60.2 ± 7.0 cm^2/m^2 for men. Prior to adjustment for weight change, WL+AT seemed to decline the most SMI_{CT} units, while WL+RT seemed to decline the least before and after adjustment for weight change (both p<0.001 between groups, Table 2); but we did not find pairwise differences in any model (p=0.45–0.82, eTable 2). Prevalence of sarcopenia as measured by SMI_{CT} was 15% (n=8) at baseline, and only half of these participants follow-up data. From the four participants with follow-up data, only one in the WL+RT group approached the threshold for becoming non-sarcopenic. Among the 30 participants that did not classify as sarcopenic at baseline, one in WL alone, two in WL+RT, and three in WL+AT had sarcopenia at follow-up. Therefore, prevalence of sarcopenia at follow-up was 29% (n=10).

3.4 Associations between Muscle and Bone Quality Measures

Intervention effects on the bone quality outcomes have been published.[11] For participants with follow-up data (n=29), baseline vBMD was 123.77 ± 35.54 mg/cm^3 and lumbar bone strength was 3.52 ± 1.08 kN. Unadjusted 18-month changes were −3.64 (−6.40, −0.87) mg/cm^3 (p=0.12) and −0.17 (−0.33, −0.01) kN (p=0.04), respectively. Baseline total hip vBMD and hip fall strength for participants with follow-up data was 299.15 ± 30.77 mg/cm^3 (n=25) and 2.02 ± 0.35 kN (n=22), respectively. Unadjusted 18-month changes were −23.83 (−29.06, −18.60) mg/cm^3 (p<0.01) and −0.03 (−0.04, −0.01) kN (p<0.01), respectively. After adjustment for sex, recruitment wave, and baseline value of the bone variable, changes in trunk muscle radio-attenuation were positively correlated to changes in bone strength of the lumbar spine (r=0.41, p=0.04, Table 3). eTable 3 presents cross-sectional associations between muscle and bone health metrics at baseline and at follow-up. At baseline and follow-up, mid-thigh muscle area was significantly associated to hip bone strength in a fall configuration (r=0.67, p<0.01 at baseline and r=0.53, p<0.01 at follow-up), although after adjusting for sex the association at baseline weakened and at follow-up it became non-significant.

4. DISCUSSION

The primary objective of this investigation was to begin to estimate the effect of exercise modality during a community-based intentional weight loss program on multiple regional CT-derived measures of muscle in older adults with obesity. Here we report that WL+RT may be more effective than either WL alone or WL+AT at consistently mitigating muscle size and quality losses. Specifically, RT was able to preserve about 2% (~3 cm^2) more trunk muscle area than AT, and about 6% (~7 cm^2) more at the mid-thigh. Although Tukey comparisons revealed no significant pairwise differences between groups at the trunk, our finding that adding RT to WL prevents muscle loss in older adults undergoing a weight loss program is in agreement with previously reported whole-body DXA outcomes for the larger CLIP-II cohort[28] and from a recent 6-month RCT.[43] Further, when matched for total weight lost, there was little difference between WL alone and WL+AT in muscle area loss at either region (expressed as a percentage from baseline, trunk: −5.4% vs. −5.3%; mid-thigh: −5.0% vs. −6.3%). Tied to the latter, six participants who were not sarcopenic at baseline were classified as sarcopenic at follow-up, as measured by SMI_{CT}. It is important to note, however, that the three participants from the WL only and the WL+RT groups that became sarcopenic had baseline SMI_{CT} just two units above the threshold (i.e., approximately 40.5 cm^2/m^2), as opposed to the three participants in the WL+AT group, which experienced sharp declines of 4–8 cm^2/m^2 (10%−12%). This muscle mass-sparing effect is perhaps not surprising considering single-mode AT does not tend to elicit muscle hypertrophy as effectively as RT,[44–48] especially in older adults with blunted anabolic response.

Our preliminary data agree with prior literature about the superior ability of WL+RT to improve the ratio of muscle to intermuscular fat lost during weight loss.[43] Findings herein also further current knowledge by suggesting that exercise, especially RT, may be able to improve muscle radio-attenuation as measured by CT (indicating less intramuscular fat) in direct comparison to WL alone. These effects are being measured even following a weight maintenance phase (months 12–18), highlighting the relevance of adding exercise to behavioral weight loss programs. The ratio of muscle to intermuscular fat area lost at the mid-thigh was 0.2:1 for WL+RT, compared with 2:1 for both WL and WL+AT. At the mid-thigh, radio-attenuation improvements were more than three times greater in WL+RT than in WL+AT (+0.70 vs +0.19 HU), although this finding must be validated with an appropriate sample size as between group differences were not statistically significant. At the trunk, modest improvements in muscle radio-attenuation were two-fold greater in WL+AT than in WL+RT (+0.68 vs +0.34 HU) and the ratio of muscle to fat lost was 2:1 for WL+RT, compared with 3:1 for both WL and WL+AT.

Effect sizes suggest that adding either AT or RT to WL preserves or slightly improves muscle quality during weight loss, as measured by muscle attenuation and intermuscular fat percentage. As to why WL+AT might have improved muscle attenuation (a measure of intramyocellular lipid content) more at the trunk and WL+RT more at the mid-thigh, one factor to consider is the site-specific nature of exercise. The machine-based RT intervention in this study included six lower extremity exercises (leg press, hip adduction, hip abduction, calf extension, leg extension, and leg curl) and two lumbar trunk-specific exercises (rotary torso and abdominal crunch), which may have influenced the dose response of RT on each body region. Another possibility is that further muscle quality improvements could have been blunted by insufficient protein intake, and therefore making the AT and RT groups more similar than they would have otherwise been. Protein intake for CLIPII was set at a minimum of 0.8 g/kg of body weight per day, with a counseled goal of 1.0g/kg/day, but more recent guidelines suggest active older adults may need at a minimum 1.2 g/kg/day.[49] Nevertheless, the protein intake counseled for this study is representative of older adult protein intake in the United States and is in line with the community weight loss setting.[50]

Other studies support the notion that exercise can improve muscle radio-attenuation.[51–53] However, exactly what magnitude change in muscle radio-attenuation is clinically meaningful is unclear. It has been observed cross-sectionally that people living with pathologies related to aging such as type 2 diabetes, obesity, and lower back pain, have lower muscle radio-attenuation by 3–15 HU when compared to participants with no obesity and absent/mild lower back pain.[54,55] In an interventional study of patients with low back pain plus disc degeneration and postlaminectomy syndrome, participants undergoing lumbar fusion experienced a decline of 6 HU at the lumbar spine after one year, while patients randomized to exercise and cognitive intervention did not experience any declines.[56] Additionally, data from cross-sectional studies suggest that older adults who are overweight have a muscle radio-attenuation 2.5 to 6 HU lower with each decade of life,[57,58] although estimates vary between reports. Furthermore, randomized studies of the effect of exercise and diet-induced weight loss on muscle radio-attenuation are lacking. Two studies have reported that older adults (65–83 years and 67–98 years) doing RT with no WL during 10–12 weeks increased their mid-thigh muscle radio-attenuation ~2 HU.[51,53] Also, older adults (76–77 years) randomized to one year of light physical activity (1.4% weight reduction) were able to preserve their muscle radio-attenuation, whereas health-education controls experienced a decrease of ~1.4 HU.[52] Finally, taken together with the findings herein, these data suggest that pathological processess may be the factor most influential to muscle radio-attenuation, that RT may be most beneficial, and that RT can expect to aim for attenuated losses, preservation, or even modest increases in muscle attenuation during weight-loss. Given that muscle radio-attenuation has been associated with muscle strength,[56,59] balance,[60] mortality,[61,62] and fall and fracture incidence,[16] investigating this association further is recommended and future appropriately powered studies with sufficient follow-up time are needed.

Low-trauma fractures are prevalent among patients with low to normal aBMD,[63] suggesting that many aspects of bone health are not being captured by traditional osteoporosis screening and that additional independent predictors and state-of-the-art techniques need to be incorporated to design and evaluate effective bone-sparing weight loss strategies. Exploratory analyses presented here suggest that there could be a positive site-specific association between changes in muscle radio-attenuation, and changes in bone strength (r=0.37–0.41) during weight loss, although this association was only significant for the trunk region. We found no association between changes in muscle area and changes in vBMD or bone strength. These findings partially contrast with previous cross-sectional studies that have reported that lower thigh muscle area and radio-attenuation are independently associated with low femoral neck BMD[64] and incident hip fracture in ages 70+,[15,65] although agreement is not absolute.[66] Further research with long follow-up times are needed to fully characterize this muscle-bone association, especially considering differences in the remodeling speed of both tissues and the metabolically dynamic environment that exercise and weight loss interventions create. If future longitudinal studies confirm the association between muscle radio-attenuation and bone strengths, then improvements in muscle quality (for example, via exercise training) could help mitigate declines in bone strength during weight loss in older adults.

Our results should be interpreted considering extensive study limitations. First, we did not evaluate the combination of AT+RT. In Waters et al., it was shown that a combined intervention of aerobic plus resistance training during weight loss resulted in an additive effect of the benefits of each modality and improves visceral adipose tissue, thigh intermuscular adipose tissue, and gait speed more than either exercise modality alone in a population of older adults with frailty.[67] However, when a single exercise modality must be adopted, the findings in this study and in Waters et al.[67] show that there was no significant difference between the effects of AT and RT in ectopic fat depot variables and that RT significantly spared the most muscle; therefore RT can be confidently prescribed in this regard. Second, there is previous evidence in older adults (70–80 years old) with limited mobility that supplementation (primarily protein) improves ectopic mid-thigh fat measures beyond the effects of physical activity alone[18] and may preserve DXA BMD during weight loss[68] but our current study did not explore this dietary quality component that may mediate the effects of exercise on muscle and bone. This ancillary study is exploratory in nature and by design, so the preliminary intervention effects found herein should be examined further and replicated in an appropriately powered confirmatory clinical trial. We cannot infer causal relationships, and the 38% loss to follow-up may have led to survivorship bias. The strengths of this study include the evaluation of bone and muscle outcomes, the RCT design, the direct comparison of different exercise modalities with a weight loss only group during community-based weight loss, a relevant sample of older adults with obesity, CVD, or metabolic syndrome, and an 18-month intervention duration.

Finally, we wish to emphasize the importance of assessing multiple musculoskeletal regions comprehensively to maximize the translation of research findings. The use of the thigh region is more established in exercise research, but the trunk region has gained traction in other fields of research such as cachexia and sarcopenia partly because it is more frequently imaged in clinical CT exams (i.e., from cancer screening and follow-up, trauma evaluation, acute pain, etc.).[69] Clarification of how exercise and/or weight loss modifies each muscle property is important to translate findings and reach agreement across studies. Correspondingly, a recent meta-analysis highlighted that an impediment to the interpretation of the effects of exercise on muscle quality in older adults is the heterogeneity of sites assessed and partial reports of muscle health.[70] In response to this gap, here we reported both muscle radio-attenuation and intermuscular fat area/percentage, and we found different intervention responses and effect sizes for these two “fat infiltration” measures. Intermuscular fat measures the fat depots between muscle fibers, while intramuscular fat is thought to indirectly measure intramyocellular fat content. From the bone health standpoint, BMD and bone strength often display site-heterogeneity, and both the hip and spine are regions of interest as they are common fracture sites associated with elevated morbidity.[71,72] Therefore, when possible, reporting comprehensive muscle metrics would optimize efforts towards consensus in musculoskeletal research.

In conclusion, this exploratory analysis suggests that in older adults living with obesity and either cardiovascular disease or metabolic syndrome, WL+RT may be more effective than WL and WL+AT at mitigating mid-thigh muscle area loss. Secondary analyses suggest that changes in muscle radio-attenuation are associated with changes in bone strength at the trunk. We recommend further study to elucidate whether causality can be inferred and to determine the underlying mechanism of this suggestive link.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- WL+RT better preserved muscle area and improved muscle quality more consistently than WL+AT or WL alone.
- Exercise, either RT or AT, may be able to improve muscle radio-attenuation as measured by CT (indicating less intramuscular fat) in direct comparison to WL alone.
- Exploratory analyses presented here suggest that there could be a positive site-specific association between changes in muscle radio-attenuation and changes in bone strength during weight loss at the trunk.
- More research is needed to characterize the associations between muscle and bone quality in older adults undertaking weight loss interventions and to determine if there is a causal link.

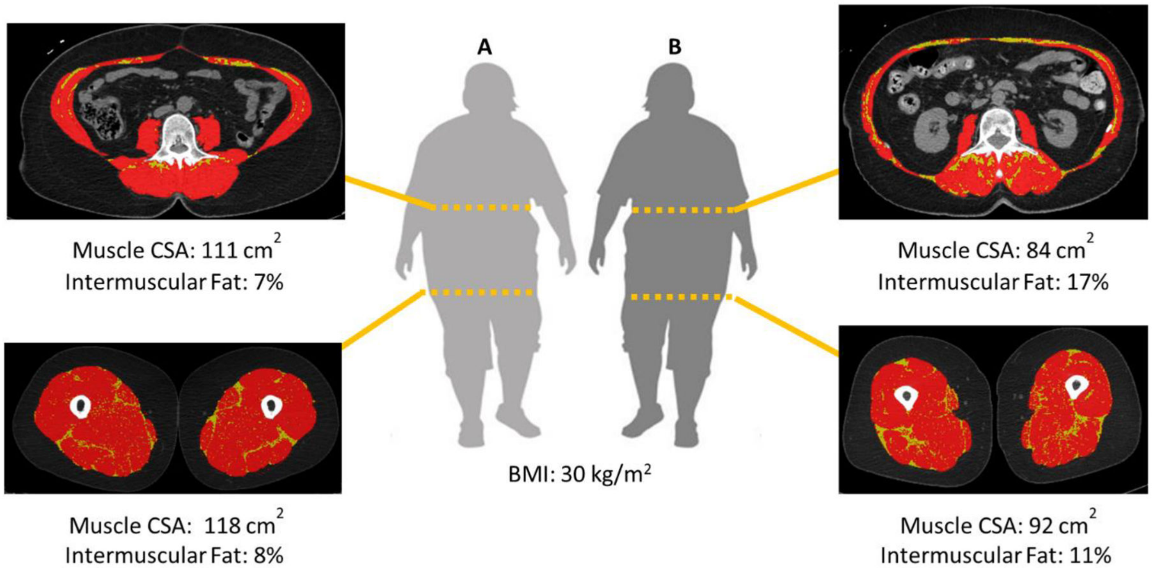

Figure 1.

Examples of trunk and mid-thigh CT segmentations. The red area highlights the skeletal muscle cross-sectional area (CSA; −29 to 150 HU) and the yellow area highlights the intermuscular fat (−190 to −30 HU).

Table 1.

Baseline descriptive characteristics and attendance data by treatment group and overall. WL=Weight loss alone; WL+AT=WL plus aerobic training; WL+RT=WL plus resistance training; kg=kilogram, m=meter. Continuous data are presented as mean (SD) and categorical variables are presented as n (%).

Baseline Variable	WL (n=17)	WL + AT (n=19)	WL + RT (n=19)	All (n=55)
Age, years	66.8 (3.9)	65.8 (5.1)	65.0 (3.8)	65.8 (4.3)
Female	11 (65)	12 (63)	12 (63)	35 (64)
Race/ethnicity				
Black	6 (35)	6 (32)	3 (16)	15 (27)
Hispanic	0	0	1 (5)	1 (2)
White	11 (65)	13 (68)	14 (74)	38 (69)
Other/Mixed/Missing	0	0	1 (5)	1 (2)
Total body mass, kg	97.8 (18.8)	93.6 (16.1)	97.0 (16.5)	96.1 (16.9)
Body Mass Index, kg/m^2	34.4 (3.6)	33.6 (3.5)	34.1 (3.7)	34.0 (3.5)
Intervention Session Attendance, %	65.9 (35.6)	75.7 (24.7)	76.8 (15.8)	73.1 (26.2)

Table 2.

Unadjusted baseline and adjusted 18-month intervention effects on computed tomography muscle metrics. WL= Weight loss alone; WL+AT= WL plus aerobic training; WL+RT= WL plus resistance training; kg= kilogram; m= meter; cm= centimeter; HU= Hounsfield unit; %= percentage. Aggregate baseline data presented as raw mean (SD). 18-month values presented as model adjusted means (95% confidence interval).

Outcome Variable	Baseline (n=55)	WL (n=9)	WL + AT (n=13)	WL + RT (n=12)	*p*-value
Trunk					
Muscle Area, cm^2	145.0 (39.5)				
Δ Model 1[a]		−5.24 (−10.54, 0.04)	−8.14 (−12.64, −3.63)	−4.97 (−9.30, −0.63)	<0.001
Δ Model 2[b]		−7.82 (−12.30, −3.35)	−7.72 (−11.36, −4.07)	−5.14 (−8.65, −1.63)	<0.001
Muscle Attenuation, HU	30.5 (7.0)				
Δ Model 1		−1.21 (−3.86, 1.43)	1.44 (−0.63, 3.51)	0.64 (−1.57, 2.85)	0.31
Δ Model 2		−0.57 (−2.84, 1.69)	0.68 (−1.12, 2.49)	0.34 (−1.53, 2.22)	0.01
Intermuscular Fat Area, cm^2	17.44 (12.1)				
Δ Model 1		−1.59 (−4.13, 0.95)	−3.61 (−5.61, −1.60)	−2.81 (−4.95, −0.67)	0.23
Δ Model 2		−2.43 (−4.43, −0.42)	−2.89 (−4.48, −1.30)	−2.55 (−4.22, −0.89)	<0.001
Intermuscular Fat, %	10.9 (5.7)				
Δ Model 1		−0.41 (−1.95, 1.12)	−1.69 (−2.90, −0.49)	−1.36 (−2.65, −0.08)	0.38
Δ Model 2		−0.85 (−2.19, 0.48)	−1.31 (−2.36, −0.25)	−1.24 (−2.34, −0.14)	0.02
SMI_{CT}, cm^2/m^2	50.3 (11.5)				
Δ Model 1		−2.54 (−4.43, −0.65)	−3.26 (−4.84, −1.68)	−2.41 (−3.97, −0.86)	<0.001
Δ Model 2		−3.32 (−4.76, −1.87)	−2.80 (−3.99, −1.60)	−2.26 (−3.42, −1.10)	<0.001
Mid-thigh					
Muscle Area, cm^2	124.6 (31.2)				
Δ Model 1		−3.94 (−9.12, 1.25)	−8.85 (−13.11, −4.60)	−0.57 (−5.10, 3.96)	0.006
Δ Model 2		−6.20 (−10.39, −2.02)	−7.84 (−11.19, −4.48)	−0.60 (−4.14, 2.94)	<0.001
Muscle Attenuation, HU	49.9 (3.4)				
Δ Model 1		−0.66 (−2.13, 0.81)	0.39 (−0.74, 1.52)	0.77 (−0.44, 1.99)	0.40
Δ Model 2		−0.45 (−1.90, 1.01)	0.19 (−0.92, 1.31)	0.70 (−0.48, 1.88)	0.25
Intermuscular Fat Area, cm^2	16.0 (7.8)				

Outcome Variable	Baseline (n=55)	WL (n=9)	WL + AT (n=13)	WL + RT (n=12)	*p*-value
Δ Model 1		−3.05 (−5.58, −0.51)	−4.83 (−6.85, −2.81)	−3.85 (−6.01, −1.69)	<0.001
Δ Model 2		−3.85 (−5.92, −1.77)	−4.17 (−5.83, −2.52)	−3.69 (−5.43, −1.95)	<0.001
Intermuscular Fat, %	11.3 (3.9)				
Δ Model 1		−1.51 (−3.27, 0.25)	−2.59 (−3.95, −1.23)	−2.73 (−4.18, −1.27)	0.05
Δ Model 2		−2.07 (−3.44, −0.70)	−2.07 (−3.13, −1.01)	−2.59 (−3.71, −1.47)	<0.001

[a] Model 1 treatment effects were estimated using a generalized linear model fit with treatment group, sex, and wave, adjusted for baseline value of each outcome. Pairwise Tukey comparisons reveal no difference among groups, except between mid-thigh muscle area changes in WL+RT and WL+AT (p=0.02).

[b] Model 2 adjusts for Model 1 and weight change. Pairwise Tukey comparisons reveal no difference among groups, except between mid-thigh muscle area changes in WL+RT and WL+AT (p=0.01).

Table 3.

Correlations between 18-month changes in computed tomography-derived muscle and bone measures during weight loss

	Δ Lumbar vBMD, mg/cm^3 (n=29)	***p*-Value**	**Δ Lumbar Compressive Strength, kN (n=29)**	***p*-Value**
Trunk				
Δ Muscle Area, cm^2	0.24 (−0.17, 0.57)	0.25	−0.11 (−0.47, 0.29)	0.61
Δ Muscle Attenuation, HU	0.33 (−0.09, 0.65)	0.12	0.41 (0.01, 0.70)	0.04
	Δ Hip vBMD, mg/cm^3 (n=25)	***p*-Value**	**Δ Hip Fall Strength, kN (n=22)**	***p*-Value**
Mid-Thigh				
Δ Muscle Area, cm^2	0.31 (−0.13, 0.65)	0.17	−0.11 (−0.54, 0.36)	0.66
Δ Muscle Attenuation, HU	0.31 (−0.13, 0.65)	0.17	0.37 (−0.10, 0.71)	0.12

Note. Δ= 18-month change; mg= milligram; cm= centimeter; kN= kilo newton; HU= Hounsfield unit; %= percentage; m= meter. Data presented as Pearson correlation estimates (95% confidence interval) adjusted for sex, wave, and baseline value of the bone variable.