

Evaluating Weight Loss-Induced Changes in Muscle and Bone: A CT Analysis of the *INVEST in Bone Health* Trial

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INTRODUCTION: Weight loss improves many obesity-related comorbidities; yet, remains controversial for older adults due to associated musculoskeletal declines and increased fracture risk. Computed tomography (CT) provides accurate, high-resolution measurement of weight loss-associated muscle and bone loss. The purpose of this study is to examine how CT-derived muscle and bone change over 6-months in a geriatric weight loss study.

METHODS: The *INVEST in Bone Health* is an ongoing interventional weight loss trial (NCT04076618) which was approved by the Wake Forest University Institutional Review Board (IRB00058279)¹. Older adults living with obesity received caloric restriction targeting 10% weight loss, with some randomized to additional resistance training (~33%) or weighted vest use (~33%). At baseline and 6-months participants underwent CT imaging with scan coverage spanning from mid-chest to ~3-cm below mid-shaft of the femurs. In each CT, synchronous calibration was performed with a Mindways phantom and QCTProTM software was used to calculate volumetric bone mineral density (vBMD). Trabecular and cortical compartmental vBMD were measured for the total hip and femoral neck regions. To assess muscle on these CTs, single slice images were extracted from the mid-L3 (identified as the midpoint of the third lumbar vertebra) and mid-thigh (identified as the mid-point of the full femoral length measured from the superior aspect of the greater trochanter to the inferior aspect of the lateral condyle) regions. Our group's machine learning algorithms^{2,3} were used to automatically segment muscle and intermuscular fat areas from these slices. Additionally, mean attenuation was measured from muscle segmentations to quantify muscle density, which is negatively correlated with fat infiltration. Statistical analyses were performed with paired T-tests and partial Pearson's correlations to explore cross-sectional (adjusted for age, sex and baseline weight) and longitudinal (adjusting for age, sex, and change in weight from baseline to 6-months).

RESULTS: The *INVEST in Bone Health* trial enrolled 150 older adults (66±5 yrs; 69% white; 25% male) who all completed CT scanning at baseline and 92% completed at 6-months. Among all participants, body weight decreased by 9% (-9.2 ± 4.9kg; p<0.01) after 6-months of the weight loss interventions. For participants who received a baseline and 6-month CT, muscle areas at L3 and mid-thigh decreased by 8.5% (-11.7 ± 22.4cm²; p<0.01) and 3% (-7.6 ± 16.3cm²; p<0.01) respectively [Figure 1]. For both regions, intermuscular fat area decreased by ~19% (Mid-thigh: -3.8 ± 4.1cm²; L3: -2.3 ± 2.7cm²; all p<0.01) and muscle density increased by ~2.5% (Mid-thigh: 0.96 ± 1.7cm²; L3: 0.95 ± 2.0cm²; all p<0.01) which is expected as muscle quality improves with less fat infiltration. For the total hip and femoral neck, trabecular vBMD decreased while cortical vBMD increased but these changes were not significant (<2% change). No significance was found for correlations between baseline or 6-month changes in muscle and bone metrics.

DISCUSSION: Loss of lean mass, including muscle, is expected with any type of weight loss intervention and we indeed observed in our cohort that significant 6-month weight loss was associated with declines in muscle mass, particularly at the abdominal region. Despite smaller muscle size, weight loss is known to positively affect muscle quality which was also evident in our cohort as fat infiltration (intermuscular fat area) decreased while muscle density was improved. We did not observe a statistically significant change in any vBMD measures from baseline to 6 months (<2%). This insignificant change over a short term period is not uncommon as previous research indicates that bone turnover and remodeling which ensues bone loss during weight loss occurs much slower compared to the weight loss associated changes of muscle and fat tissues. As a result, the lack of significant correlations between muscle and bone outcomes may be a result of this short-term period in which we have not yet elicited substantial bone losses.

Although the *INVEST in Bone Health* trial is a 12-month weight loss study, this work includes only analysis of CTs at baseline and 6-months since the trial is ongoing. As the trial completes CT scanning after 12-months of weight loss, this analysis will be extended to encompass changes over a longer period of time which may reveal more significant effects on bone and the subsequent correlations between bone and muscle measures. Full interpretation of our results is limited due to the lack of analysis by intervention (i.e. resistance training or weighted vest use) as these remain blinded at this time until completion of the study (expected March 2024). Future work will explore the possible interventional effects on muscle and bone CT outcomes included in the present study.

SIGNIFICANCE/CLINICAL RELEVANCE: The fully automated CT muscle processing used in this work offers a "standardized way to interpret CT to assess muscle size and quality", which is responsive to Research Needs of the *NIA & American Geriatrics Society "Osteoporosis & Soft Tissue (Muscle/Fat) Disorders" Conference*,⁵¹ and could provide opportunistic assessments by integration of these automated methods into routine CT scans. The preliminary and continued future work in the *INVEST in Bone Health* trial will provide valuable insight on the complex interplay between muscle and bone in response to weight loss and help further identification of a safe, effective therapeutic alternative for older adults living with obesity.

REFERENCES: [1] Miller et al. 2021, PMID: 3363135 [2] Barnard et al. 2019, PMID: 31326311 [3] Lenchik et al. 2021, PMID: 32504466

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