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SPATIAL HETEROGENEITY IN THE RESPONSE OF THE PROXIMAL FEMUR TO TWO LOWER-BODY RESISTANCE EXERCISE REGIMENS

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Abstract

Understanding the skeletal effects of resistance exercise involves delineating the spatially heterogeneous response of bone to load distributions from different muscle contractions. Bone mineral density (BMD) analyses may obscure these patterns by averaging data from tissues with variable mechano-response. To assess the proximal femoral response to resistance exercise, we acquired pre- and post-training quantitative computed tomography (QCT) images in 22 subjects (25-55 years, 9 males, 13 females) performing two resistance exercises for 16 weeks. One group (N=7) performed 4 sets each of squats and deadlifts, a second group (N=8) performed 4 sets each of standing hip abductions and adductions and a third (COMBO) performed two sets each of squat/deadlift and abduction/adduction exercise. Subjects exercised three times weekly, and the load was adjusted each session to maximum effort. We used voxel-based morphometry (VBM) to visualize BMD distributions. Hip strength computations used finite element modeling (FEM) with stance and fall loading conditions. Cortical and trabecular BMD, and cortical tissue volume employed QCT analysis. For muscle size and density, we analyzed the cross-sectional area (CSA) and mean Hounsfield Unit (HU) in the hip extensor, flexor, abductor and adductor muscle groups. While SQDL increased vertebral BMD, femoral neck cortical BMD and volume, and stance hip strength, ABADD increased trochanteric cortical volume. The COMBO group showed no changes in any parameter. VBM showed different effects of ABADD and SQDL exercise, with the former causing focal changes of trochanteric cortical bone, and the latter showing diffuse changes in the

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femoral neck and head. ABADD exercise increased adductor CSA and HU, while SQDL exercise increased the hip extensor CSA and HU. In conclusion, we observed different proximal femoral bone and muscle tissue responses to SQDL and ABADD exercise. This study supports VBM and vQCT to quantify the spatially heterogeneous effects of types of muscle contractions on bone.

INTRODUCTION

Muscle contractions induce high strain magnitudes in regions of bone tissue that are associated with net bone formation[1,2]. Resistance exercise has thus been widely explored as a clinical intervention in situations of disuse bone loss such as long-duration spaceflight[3] or prolonged bedrest[4] to reduce or prevent bone loss by replacing loads. For the same reasons, resistance exercise is also considered a means of attenuating the effects of age-related bone loss[5]. The proximal femur is one of the most clinically-relevant skeletal sites due to high rates of age- and disuse-related bone loss, and the high incidence of life-threatening fractures in the elderly population. Prior studies of this anatomical region primarily used areal bone mineral density (aBMD) measured by dual x-ray absorptiometry as a skeletal endpoint. Studies of lower body resistance exercise effects on proximal femoral aBMD in healthy ambulatory subjects have yielded variable results, with most studies ranging from no detectable effect to small increases in aBMD depending on the exercise protocol and the age of the subjects[6].

The variable and generally weak effects of resistance exercise on aBMD may be related to the fact that an integral BMD measurement in the femoral neck or trochanter averages large volumes of cortical and trabecular bone tissue that may mask spatially heterogeneous mechano-responses. Spatial heterogeneity in mechano-response may be associated with spatial variations in the mechano-sensitivity of bone tissue as well as heterogeneity in the strain fields induced by different muscle loads. CT imaging has the potential to address this issue by acquiring three-dimensional data that allows full depiction of geometric and sub-regional density variations as in response to changes in mechanical loading. Previous studies using CT have documented the spatial heterogeneity in proximal femoral bone loss and recovery in relation to changes in skeletal loading in long duration space missions[7,8]. Although CT densitometry has been employed to quantify the effect of squat and deadlift exercise on the proximal femur, this approach has not been employed to evaluate changes in the proximal femur associated with different types of resistance exercise. Here we extend the method to evaluate outcomes due to hip abduction and adduction exercise.

The goal of our study was to examine the spatially heterogeneous response of the proximal femur to two different lower-body resistance training regimens expected to generate distinct loads on the proximal femur: standing hip abduction and adduction and a combination of squatting and deadlifts. A previous study showed that standing unloaded hip abduction and adduction exerted peak loading forces on the proximal femur that approached 4 body weights[9], approximately twice those exerted by body-weight squatting exercise[10]. Because of the magnitude of these forces, and the fact that they are oriented along axes in which the hip is not typically loaded in physiologic conditions, we hypothesized that abductor and adductor training would have a spatially distinct and larger osteogenic effect than squats and deadlifts. To test this hypothesis, we conducted a training study, using pre- and post-training CT measurements to compare the effects of the exercises on proximal femoral density. To evaluate the spatial heterogeneity of the skeletal response to exercise, we processed the CT images with a technique newly applied by our group to the study of bone, voxel-based morphometry (VBM)[11], which allowed us to examine subject-to-subject differences on a voxel level.

METHODS

Subjects

24 healthy adult male and female subjects (age range 25 to 55 years) were enrolled in the study. Exclusion criteria for the study were: hypertension, diabetes or metabolic syndrome, high cholesterol, cardiovascular disease, asthma or any other pulmonary disease, participation in an exercise regimen in the last 12 months, pregnancy or plans to become pregnant during the course of the study, joint disability or mobility limitations, and recommendation by a physician not to participate in exercise. There were no exclusion criteria regarding menopausal status, or use of bone-active medications, such as anti-osteoporosis medications, glucocorticoids, or birth control medications, or hormone replacement medications. Before providing informed consent according to the procedures of the Committee on Human Research at the University of California, San Francisco, the subjects underwent a screening interview to determine eligibility for the study.

Exercise Protocol

Subjects underwent a 16-week exercise regimen in which they reported to the exercise laboratory three times per week (Monday, Wednesday and Friday) for a ~45 minute training session. The subjects were randomized into three groups. Exercise followed a five-minute warm-up session on an exercise bicycle. The standing hip abduction/adduction (ABADD) group completed 4 sets each of standing hip abduction and adduction. In order to reduce the engagement of the trunk muscles for standing ABADD, the subjects were asked to brace themselves with their arms against the vertical stanchion of the exercise machine. If the subject was observed by the exercise physiologist to use excess momentum to assist in the ABADD exercise, they were coached not to do so, and the weight was adjusted downward if the subject was unable to comply. The squat/deadlift (SQDL) group completed 4 sets each of squats and deadlifts, and the combination Group (COMBO) carried out 2 sets of abduction/adduction and squat/deadlift exercise, keeping the total number of contractions the same as for the ABADD and SQDL groups. For all three groups, we employed a standard periodization protocol used for beginning weightlifters, with the number of repetitions for the ABADD and SQDL groups varying throughout the week, with 10 per set on Monday, 6 per set on Wednesdays and 8 per set on Fridays. Initial load for each exercise was effectively set by trial and error. In the first 2-3 training sessions, the load was adjusted such that on the 10-rep day the subject reached or came close to volitional fatigue at the 10th repetition, and followed the same format for the 6 and 8 repetition days. Progressive overload was achieved as follows. As the subject became able to complete the assigned repetitions (based on the exercise physiologist's observations combined with feedback from the subject), resistance was adjusted upward until the desired number of repetitions became close to or at volitional fatigue at the completion of the final repetition. This pattern continued throughout the training study. Subjects rested two minutes between sets and, on each day of exercise, the load was adjusted so that the subjects would exercise to failure by the end of each set. The exercise motions and a summary of the protocol are shown in Figure 1. For each subject, the maximum achieved loads for the assigned exercises were recorded at each session.

Serum Bone Marker Analyses

Blood draws (5 ml) were taken from each subject at the beginning and end of the study, and in the fourth, eighth and twelfth weeks, to assess serum markers of bone formation (osteocalcin) and resorption (CTX Type I). Measurements were taken mid morning, on a day in which the subjects did not exercise.

CT Imaging

Subjects underwent volumetric quantitative CT imaging (vQCT) of the spine and hip using protocols established at our facility. In the spine study, the subjects had a volumetric scan of the L1 and L2 vertebrae (120 kVp 150 mAs, 2.5 mm slice thickness, 50 cm field of view, 0.976 mm in plane voxel size, standard reconstruction algorithm), and a volumetric scan of the proximal femora (between the superior aspect of the acetabulum and the inferior aspect of the lesser trochanter) using the same scan parameters. To calibrate the CT image units to equivalent values of volumetric bone mineral density (vBMD), the subjects lay supine atop a calibration phantom (Image Analysis, Columbia, KY, USA).

vQCT Image Analyses

Images were analyzed to obtain three sets of endpoints: vertebral and proximal femoral volumetric integral (all bone within the periosteal bone envelope), cortical and trabecular bone mineral density (vBMD), proximal femoral strength, proximal femoral bone mineral density distribution, and the cross-sectional area and attenuation coefficients (measures of tissue adiposity) of the hip extensor, abductor, adductor and flexor muscle groups.

vBMD Analyses

For vBMD measurements of the spine and hip, we employed an algorithm which has been employed in studies of spaceflight and mechanical unloading, and which has been thoroughly described by Lang et al[7,8]. In the hip, cortical, trabecular and integral vBMD was measured in the femoral neck, trochanter and in a total femoral region which encompassed the femoral neck and trochanteric regions. In the spine, vBMD was measured in the anterior portion of the vertebral body trabecular bone, in a 10-mm thick mid-section of the vertebra, and in a region containing all of the vertebral bone excluding the transverse processes. Regions for vBMD analysis are shown in Figure 2.

Bone Strength Analyses

In addition to vBMD, estimates of computed bone strength of the hip were calculated using finite element modeling (FEM) techniques for all study subjects[12-15]. Loading conditions representing either single-limb stance or a fall onto the posterolateral aspect of the greater trochanter were modeled and FEM strength values were expressed as a percentage change from baseline. Single-legged stance strength estimates were computed using nonlinear modeling techniques that have been previously described[12]. Computed bone strength estimates for fall loading also were conducted using nonlinear modeling using a method developed by Keyak et al[15]. In addition to the whole bone strength by finite element modeling, we computed the torsional rigidity of the cross-section of minimal area of the femoral neck, and the axial compressive strength indices of the same section of the femoral neck and the mid-section of the vertebral body[7].

VBM

To compute changes in vBMD on a per voxel level, we employed VBM, a technique developed to visualize detailed morphological alterations of the brain for MRI, and adapted to the study of structural variations of bone by our group[11,16,17]. The method applied in this study to generate an atlas of pre- and post-exercise scans was recently described in detail by Carballido-Gamio et al [11]. In short, all images from our subjects, both pre- and post-exercise training, were registered to a single template derived from a young population of Caucasian women forming an atlas of the study[11]. Within each voxel of the atlas, the paired t-test was carried out between pre- and post-exercise time points, with adjustments for multiple comparisons using false discovery rate (FDR). Because of the small number of subjects, and the high variability of vBMD changes in a per voxel basis, individual voxels showed no significant changes. Therefore, a cluster-based analysis was performed[18]. To carry out this analysis, we employed the atlas to compute pre- and post-training mean images for both the ABADD and SQDL groups. For each group, the mean baseline image was subtracted from the mean follow-up image to generate a difference image. From these difference images, clusters of at least 35 contiguous elements that showed a change in vBMD greater than or equal to 15 mg/cm^3 were identified. The 15 mg/cm^3 threshold was chosen to reduce the effect of image noise, based on histograms of vBMD values in cortical bone regions in representative scans from the study. The cluster size of 35 contiguous elements was chosen as a value which was large enough to reduce the impact of the high voxel-level variability in the difference, while still being small compared to the anatomic scale of the proximal femur (0.03 cm^3 volume compared to the 7-9 cm^3 volume of the femoral neck cortical region in the vQCT analyses). Clusters that occurred in regions that were associated with severe partial volume averaging, such as those located at the exterior cortical margin, or in other regions such as the superior aspect of the greater trochanter were rejected as being influenced by artifacts. Although some clusters showed negative changes, these occurred only in these suspect regions, and thus our analysis was limited to clusters that showed positive changes. Once the clusters of voxels were determined for each exercise group, we calculated for each subject the mean vBMD in each cluster pre- and post-exercise and compared them based on paired t-tests followed by FDR correction for multiple comparisons (q=0.05). Because the ABADD and SQDL exercises should produce fundamentally different patterns of loading on the proximal femur, we conducted the VBM analysis for only the ABADD and SQDL groups. The VBM analysis software was developed in-house using MATLAB (The Mathworks Inc. Natick, MA).

Hip Muscle Analysis

To evaluate the effect of exercise on the size and fatty infiltration of the hip muscles, we employed a method developed at our laboratory to assess the lean areas and lean tissue attenuation coefficients, which reflect the fatty infiltration of skeletal muscle[19,20] of the hip extensors, hip abductors, adductors and flexor muscles, according to previously published methods[21]. An overview of the quantified muscles is shown in Figure 3. Briefly, three 10-mm thick cross-sections are reconstructed from the volumetric scan. A cross-section at the level of the mid-femoral neck is employed to measure the hip extensors, which is taken as the fascial plane of the gluteus medius. At the level of the mid-femoral head, the outlines of the hip abductor muscles are drawn. At the level of the lesser trochanter, we define the hip adductors and the hip flexors. As described in Lang et al[21], once the fascial planes are defined, Hounsfield Unit intervals are applied to separate the adipose and non-adipose tissues within the fascial planes. The three parameters of interest include the cross-sectional area (CSA) of lean tissue within each group and the mean CT attenuation coefficient (HU) of the lean tissue. The latter value has been shown to be a measure of lipid content in and around the muscle fibers, consisting both of extramyocellular lipid contained within local adipocytes and intramyocellular lipid, consisting of triglyceride on and around the fiber cell membranes. The lean-tissue HU is positively correlated with muscle strength independently of the CSA, and lower values of this measure have been associated with mobility limitations[22] and incident hip fractures in the elderly[23].

RESULTS

Of the 24 subjects who began the training study, 22 completed their entire training program (ABADD, n=8; SQDL, n=7; COMBO, n=7). The characteristics of these subjects are displayed in Table 1. The ABADD group showed a 51% increase in 10-repetition maximum load for both abduction and adduction ($p<0.001$), and the 10-repetition maximum load of the SQDL group increased by 64% for both squat and deadlift ($p<0.010$. In the COMBO group, the 10-repetition maximum loads for both abduction and adduction increased by 37% ($p<0.001$), and those for squats and deadlift both increased by 35% ($p<0.01$).

Bone Markers

Neither serum marker of bone metabolism changed from pretraining baseline to post-training in any of the groups.

vQCT Bone Density and Structure

vQCT vBMD and structure parameters are summarized in Tables 2 and 3. The skeletal response to 16 weeks of resistance training varied by exercise modality. The ABADD group showed an increase in the volume of the trochanteric cortical region of interest (4.1%, $p<0.01$), but no significant changes in any other parameters. The SQDL group showed changes localized to the femoral neck, with increased integral vBMD, cortical vBMD and cortical volume (1.6%-3.4%, $p<0.05$). The SQDL group also showed increases in vertebral integral vBMD (3.1% $p<0.05$) and spinal trabecular vBMD (7.0%, $p<0.05$). The COMBO group showed no changes from baseline in any bone parameter.

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vQCT Bone Strength

Neither the ABADD or COMBO groups showed any statistically significant increases from baseline in any measure of bone strength (Table 3). On the other hand, the SQDL Group showed 4.6% and 4.7% increases in BMD- and modulus-weighted femoral neck torsional strength ($p<0.05$), as well as a 9% increase in whole hip strength assessed by non-linear FEM in the stance loading condition. No change from baseline was observed for FEM in the fall loading condition.

VBM

Results of voxel-based morphometry are shown for the ABADD and SQDL groups in Figure 4. For both groups, the difference map indicates that statistically significant changes mostly occurred in the cortical bone and that the distribution of change varied by exercise protocol. The ABADD group showed changes that were primarily localized at the greater trochanter, whereas the changes in the SQDL group were primarily observed in the femoral neck and head. The femoral head changes in the SQDL group were concentrated in the trabecular compartment.

Hip Muscle Analysis

The ABADD group showed increases in the lean CSA and lean tissue HU of the adductor muscle (7.4% and 2.5%, both $p<0.05$), and of the abductor lean tissue HU (2.1%, $p=0.05$) but not the lean CSA. In comparison, the SQDL group showed increases in the extensor lean CSA and HU (6.5% and 3.0%, $p<0.05$), but not in any of the abductor or adductor variables. No changes from baseline were observed for the COMBO group.

DISCUSSION

Our study was novel in several aspects. To the best of our knowledge, it was the first longitudinal study to use vQCT to distinguish the effects of two different modes of lower body resistance exercise on the proximal femur and the surrounding musculature. In this study, sixteen weeks of resistance training resulted in changes in skeletal density, geometry and strength that varied by the mode of exercise. Even with a relatively small sample size, the use of vQCT allowed us to evaluate the trabecular and cortical bone envelopes, to determine their spatial distribution of skeletal changes, and to examine effects of the exercise on the area and density of the adjacent muscle groups.

Within the proximal femur, the effects of exercise were limited to the cortical compartment, with no detectable effect on trabecular bone. In squatting/deadlift exercise, the femoral neck is primarily loaded in bending, and this is consistent with the observed increases in cortical bone density and volume, as observed by vQCT and VBM analysis, that were primarily localized to the cortical bone in the femoral neck. These changes may result from the large bending loads exerted by SQDL exercise on the femoral neck, which would tend to induce bending stress on the inferior cortex and tensile stress on the superior cortex. The cortical focalization of femoral neck density increases likely contributed to the observed increases in proximal femoral whole-bone strength in stance loading and to the density-weighted torsional strength index, two measures that are highly weighted by the density values of the cortical elements. The VBM analysis, in addition to showing increased bone density in the femoral neck, also showed small focal increases in the femoral head and the greater trochanter. The changes observed in the femoral head approximately aligned with the principal compressive trabecular band, which is subject to axial loads in SQDL exercise. The greater trochanter is the attachment site of the hip abductors. The abductor muscles contract to provide balance during the squatting motion, and thus would be expected to exert heavy loads at the trochanter.

Compared to the squatting/deadlift exercise, which was associated primarily with changes in femoral neck density, the abductor/adductor exercise produced changes that were mostly localized to the greater trochanter, the primary attachment site of the hip abductors. A small region of change was observed by VBM analysis at the lesser trochanter, which is the most proximal insertion point of the hip adductors. Unlike SQDL training, which produced increased cortical vBMD at the femoral neck, the abductor/adductor training resulted in an increase in the volume of cortical bone in the trochanteric region of interest. While the new cortical bone was detected both with standard region-of-interest analysis and with VBM, it did not translate to an increase in total femur strength as measured by FEM in either loading condition. The relatively weak response of the skeletal tissue to the abductor/adductor exercise in comparison to the femoral neck effects was at variance with the previous data from the Orthoload Project showing that, when body-weight squat/deadlift and abduction/adduction exercise was carried out, peak loads of approximately 4-6 times body weight were generated from unloaded ad/ab exercise, roughly twice the peak loads measured from squatting exercise[9]. The discrepancy between the large forces expected to be exerted on the proximal femur based on previous evidence, the changes visible with VBM, and the lack of a strength response by FEM, might be due to the possibility that the cortical elements that change as a result of abductor/adductor exercise may not be those elements which are involved in the failure process modeled by FEM. Alternatively, it is important to note the limitations to the use of instrumented hip prostheses as employed by the Orthoload project, which are based on a limited number of strain gauges placed on the inferior inner margin of the femoral neck. Obtaining a better understanding of this issue points to the need for further studies of muscle effects on bone strength using more sophisticated instrumentation and FEM modeling techniques.

An interesting result of our study was that, similar to a previous study of SQDL exercise reported by Loehr et al[24], trabecular BMD in the femoral neck and trochanteric regions of interest did not respond to either SQDL. The lack of trabecular bone effect at the hip observed densitometrically by vQCT in these regions for both SQDL and ABADD exercise seems at variance with the high sensitivity of trabecular bone to mechanical unloading in bedrest and spaceflight[7], where loss of trabecular bone density in femoral neck and trochanteric regions of the proximal femur is among the highest of all skeletal sub-regions. It is also at variance with the large effect observed in the SQDL group at the spine both in our study and in Loehr et al[24]. In contrast, using VBM, we observed clusters of increased femoral head trabecular BMD in the SQDL group. The principal compressive band, one of the primary load bearing structures in the hip, fans out in the femoral head, and is likely to have sustained large increases in loading due particularly to the squatting component of the SQDL exercise. Only a small part of this trabecular band is sampled in the other regions of interest, which may partially account for their low responsiveness to the exercise regimens. Moreover, the femoral neck and trochanteric regions are rich in cortical bone, which shares in load bearing and in fact showed exercise-related changes in our study.

Of particular interest in this study is that it was the first to use VBM to delineate the distinct skeletal effects of two different types of exercise. The response of bone to exercise is a function of the pattern of load bearing, i.e. variation in stress-strain fields, associated with the activity, which vary three dimensionally throughout the proximal femur. These patterns of change may not necessarily correlate with an approach that focuses on anatomically determined regions such as those delineated byDXA or vQCT. Thus, a data driven approach such as ours, which interrogates the whole image, without bias, may be useful for delineating the osteogenic effect of specific exercises and correlating these effects to the mechanical loads imposed. This may reduce the needed sample size, as well as provide better correlative information for understanding of finite element models.

The sixteen week period of exercise training did not result in changes in serum CTX type I or osteocalcin in any of the three groups at any time point. There is inconclusive evidence in the literature for long-term training effects on markers of bone metabolism. Two studies in young women failed to observe changes in either osteocalcin or CTX in response to resistance exercise [25,26] while a study in young men found evidence for increased levels of osteocalcin but no changes in CTX[27], and another study of a gender mixed cohort undergoing a protocol similar to ours found no evidence for changes in bone metabolic markers[24].

As expected from previous studies examining the effect of knee extension and flexion on the mid-thigh musculature, resistance training increased the cross-sectional area and HU of the hip muscles involved in the specific training modes carried out in the study[28]. Squat deadlift exercise resulted in increased cross-sectional area and HU of the hip extensor muscle group (gluteus medius), the primary muscles trained in squatting. On the other hand, hip abduction and adduction resulted in significant changes in the HU of the hip abductor muscle, and robust increases in the area and density of the adductor muscle. This is consistent with the use of these muscles in everyday life. Abductor muscles serve primarily as stabilizers and are heavily used, and thus the ABADD exercise as carried out may not produce a large effect. On the other hand, hip adduction is not a common activity, and thus these relatively weak muscles may be significantly affected by our training program, which involved substantially higher muscle loads than would be expected from normal usage.

Another surprising finding of our study was that 16 weeks of COMBO exercise did not produce any effects in any bone or muscle variables. In our study, subjects did the same number of repetitions for each type of exercise, and thus for the COMBO group, each subject did half the number of each particular motion as subjects in the SQDL and ABADD groups. It is possible that the reduction in the number of muscle contractions per exercise fell below a threshold required for an osteogenic or myogenic effect. Another potential contributing factor was that the average age of the COMBO group showed a trend to be higher than those of the ABADD or SQDL groups, although this age difference was not statistically significant (p=0.09).

This study had both strengths and limitations. The strengths of the study included the use of two distinct exercise protocols, the high compliance level of the subjects, and the comprehensive imaging protocol assessing bone density, geometry, strength and bone mineral distribution, as well as muscle size and density of the relevant hip muscles. We attempted to make the squat and deadlift protocol, and the subject composition, as similar as possible to a previous study that had QCT monitoring and this is reflected in the similarity of our spine results to theirs[24]. Limitations of the study were the small sample size, which reduced the effect size that we could observe, as well as the ability to draw comparisons between genders. We did not control for menopausal status, and inclusion of post-menopausal women may have resulted in diminished effect of exercise caused by loss of skeletal mechanosensitivity. Similarly, we did not exclude subjects using bone-active medications such as glucocorticoids, hormonal contraception or hormone replacement therapy. Another limitation was the relatively short length and low exercise intensity of the training program, which reduced the magnitude of the exercise effect. The CT imaging protocol was limited due to partial volume averaging effects, which reduce apparent cortical bone density and may have diminished our ability to detect an exercise response for cortical bone. In particular, partial volume averaging errors made it difficult for our study to distinguish between changes in cortical density and cortical thickness or volume. For example, our observation of a marginally significant increase in femoral neck cortical volume in the SQDL group may have been the result of an increase in femoral neck cortical BMD. Finally, our muscle quantification approach was based on reconstructing relatively thin cross-sections of the considered muscle groups in the field of view of the CT scans. The combination of a hip CT scan which included sub-volumes of the muscles, and the analytic approach, which assessed CSA and HU in cross-sections of those sub-volumes, provided relatively limited samples of these muscles, and we thus could not detect local variations of exercise related changes in muscle tissue.

In conclusion, we found that resistance training resulted in distinct changes to muscle and bone tissues as quantified by several QCT derived analytical techniques. Effects of squat/deadlift and abductor adductor exercise were localized respectively within the femoral neck and trochanter, and both were primarily centered on cortical rather than trabecular BMD, although trabecular bone at the spine responded robustly to exercise.

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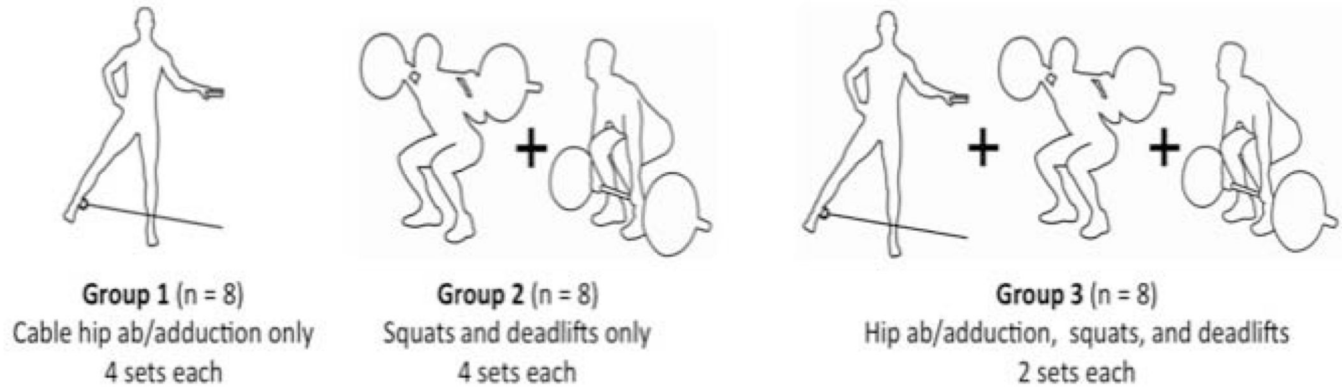

Figure 1.
SQDL, ABADD and COMBO exercise groups.

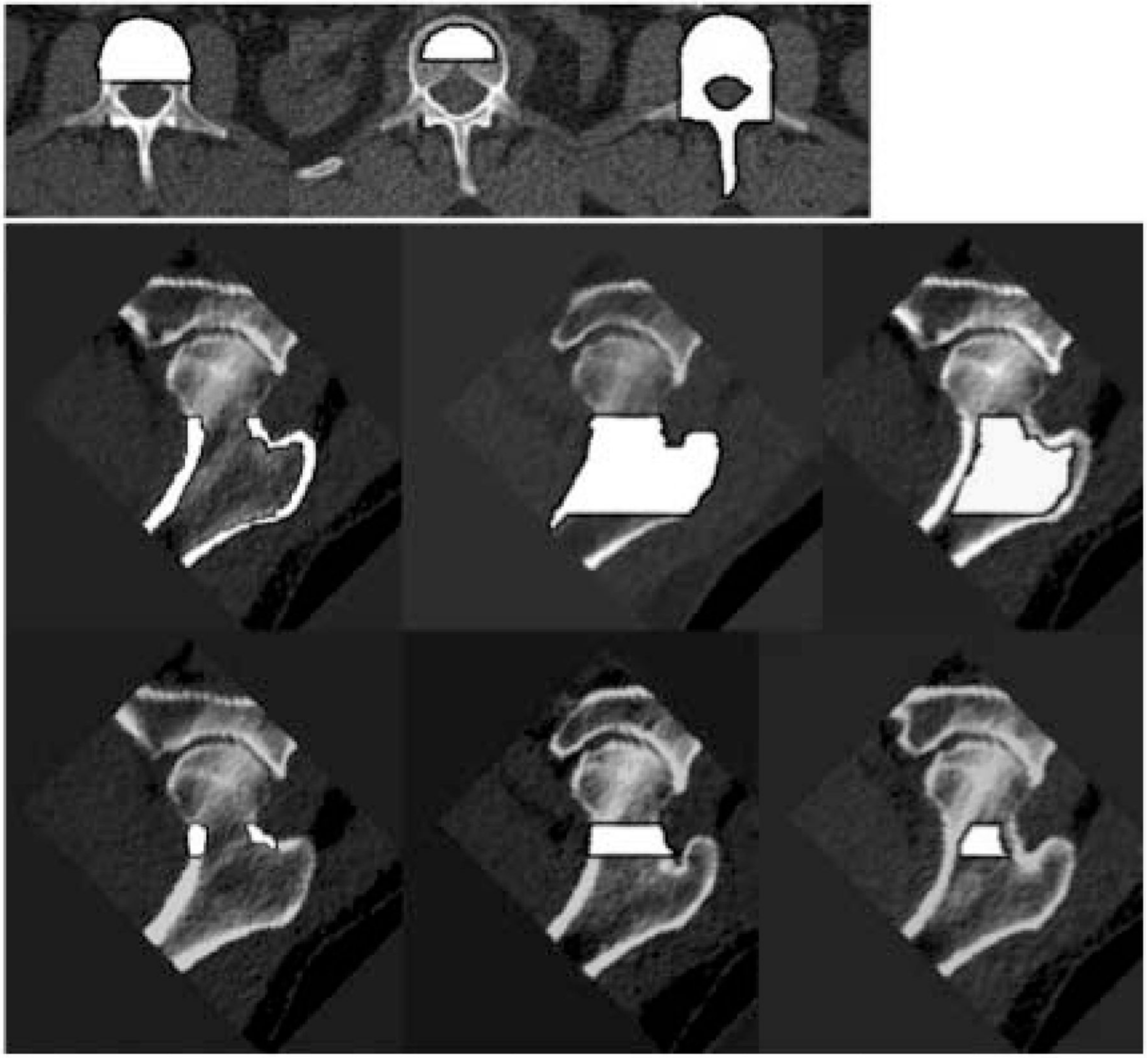

Figure 2.

Regions for densitometric assessment. Top row (left to right): vertebral centrum integral, trabecular and total integral regions of interest. Middle row (left to right): Total femur cortical, integral and trabecular regions of interest. Bottom row (left to right): Femoral neck cortical, integral and trabecular regions of interest.

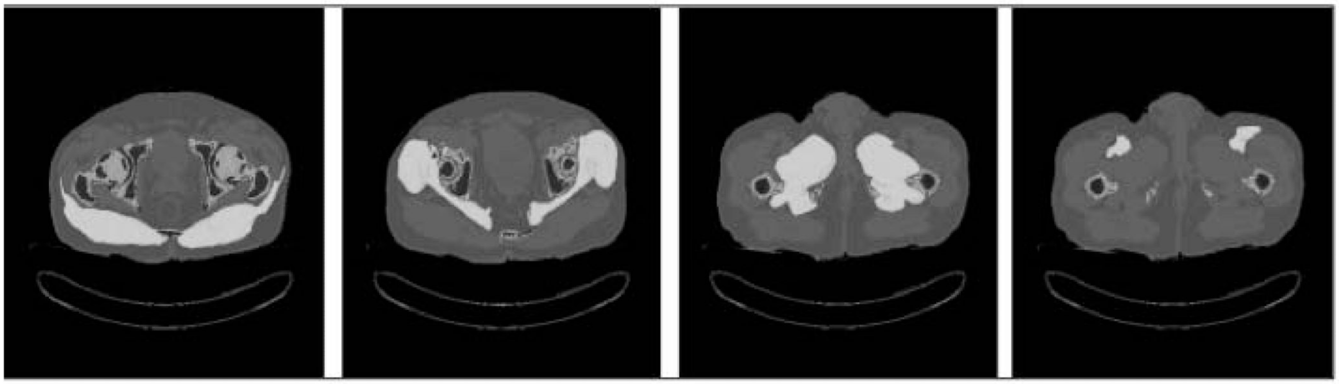

Figure 3.
Hip muscle regions of interest Left to right: white regions show hip extensors, abductors, adductors and flexors

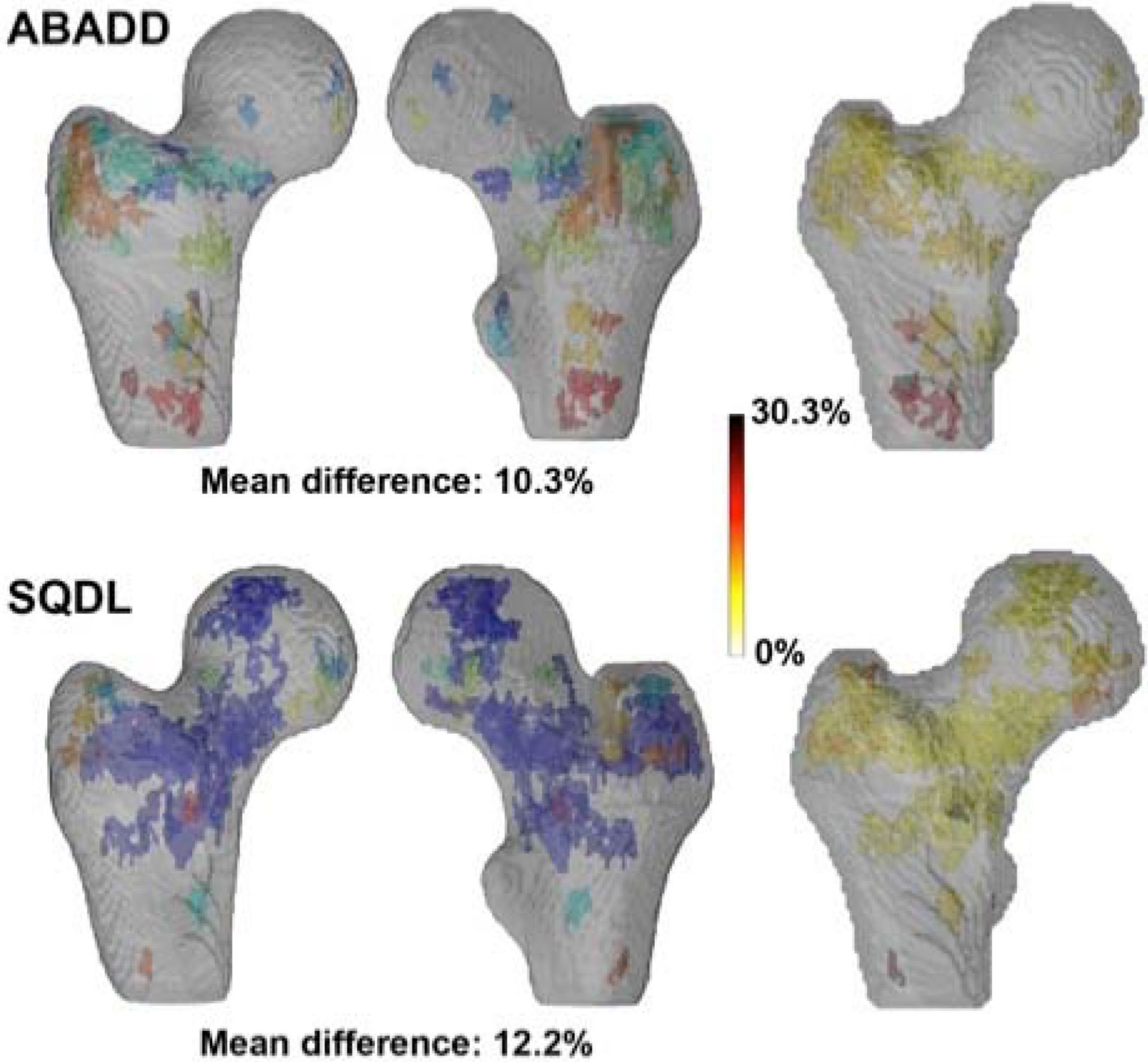

Figure 4.

Clusters of voxels identified as significantly different between baseline and 16 week visits by voxel based morphometry. These voxel clusters met criteria for statistically significant change (at least 35 contiguous voxels with vBMD change ≥ 15 mg/cm3). Left: Anterior view, showing distinct clusters of voxels, with each cluster identified by a different color. Middle: Posterior view of statistically significant clusters. Right: Posterior view of distribution of percentage differences with magnitude of difference denoted by scale bar.

Table 1

Descriptive characteristics of exercise cohort

Group	N/Gender	Age Years (SD)	Height (m) (SD)	Weight (kg) (SD)
AbAdd	3 male 5 female	38.0 (7.6)	1.68 (0.13)	69.9(12.6)
SQDL	3 male 4 female	36.1 (10.0)	1.72 (0.16)	74.9 (20.9)
COMBO	3 male 4 female	45.1 (4.6)	1.69 (0.06)	76.9(10.1)

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Table 2

Mean values (standard deviations) of bone density variables compared pre- and post-training for AbAdd, SQDL and COMBO groups.

	Femoral Neck Integral vBMD	Femoral Neck Cortical vBMD	Femoral Neck Trabecular vBMD	Trochanteric Integral vBMD	Trochanter Cortical vBMD	Trochanter Trabecular vBMD	Spinal Trabecular vBMD
ABADD							
Pre-Training	0.305 (0.064)	0.515 (0.040)	0.131 (0.074)	0.285 (0.059)	0.529 (0.041)	0.138 (0.049)	0.170 (0.053)
Post-Training	0.305 (0.062)	0.519 (0.032)	0.127 (0.072)	0.286 (0.057)	0.530 (0.042)	0.139 (0.049)	0.168 (0.056)
SQDL							
Pre-Training	0.322 (0.041)	0.528 (0.040)	0.143 (0.074)	0.306 (0.036)	0.549 (0.029)	0.147 (0.045)	0.172 (0.046)
Post-Training	0.327* (0.039)	0.537* (0.042)	0.144 (0.071)	0.307 (0.034)	0.551 (0.023)	0.147 (0.044)	0.185* (0.040)
COMBO							
Pre-Training	0.318 (0.056)	0.517 (0.032)	0.163 (0.061)	0.309 (0.055)	0.530 (0.038)	0.164 (0.054)	0.194 (0.050)
Post-Training	0.316 (0.052)	0.521 (0.027)	0.165 (0.063)	0.312 (0.055)	0.535 (0.038)	0.147 (0.044)	0.195 (0.044)

* significant difference (paired Students T-Test, $p<0.05$) between pre-training and post-training time points.

Table 3

Mean values (standard deviations) of bone structure and strength variables compared pre- and post-training for AbAdd, SQDL and COMBO groups

	Femoral Neck Cortical Volume	**Trochanter Cortical Volume**	**Femoral neck bending strength index**	**Femoral neck axial compressive strength index**	**FEM Fall Strength**	**FEM Stance Strength**	**Vertebral compressive strength index**
ABADD							
Pre-Training	14.4 (1.3)	48.7 (5.7)	1648 (448)	1.003 (0.270)	4260 (517)	11218 (1711)	0.310 (0.119)
Post-Training	14.9 (0.8)	50.7** (5.1)	1674 (468)	0.990 (0.244)	4283 (645)	11217 (1357)	0.303 (0.129)
SQDL							
Pre-Training	17.6 (4.9)	59.8 (15.8)	1927 (724)	1.207 (0.397)	4363 (524)	12874 (3551)	0.325 (0.137)
Post-Training	18.2* (5.6)	60.0 (15.9)	2006* (747)	1.258* (0.374)	4417 (665)	13917* (3345)	0.364* (0.123)
COMBO							
Pre-Training	15.9 (3.2)	51.2 (10.7)	2143 (519)	1.32 (0.44)	4837 (791)	14309 (2985)	0.417 (0.197)
Post-Training	16.3 (3.2)	55.4 (10.0)	2154 (554)	1.33 (0.47)	4417 (665)	14543 (3439)	0.412 (0.123)

* significance of differences between pre- and post-training values (Students T-test). *: $p<0.05$;

** $p<0.01$

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Table 4

Muscle CSA and HU compared pre- and post-training for AbAdd and SQDL groups

	Extensor CSA (HU)	**Flexor CSA (HU)**	**Abductor CSA (HU)**	**Adductor CSA (HU)**
ABADD				
Pre-Training	74.3 (17.1) **17.4 (16.0)**	5.5 (1.5) **32.6 (7.4)**	67.5 (5.6) **36.9 (7.1)**	79.4 (9.6) **45.7 (3.8)**
Post-Training	72.1 (19.5) **20.5 (14.4)**	5.7 (1.4) **31.6 (7.8)**	67.6 (5.9) **37.4 (7.4)***	84.5 (12.2)*** **47.8 (3.4)***
SQDL				
Pre-Training	103.2 (29.7) **42.8 (7.6)**	7.6 (3.6) **39.1 (4.0)**	64.8 (19.2) **36.9 (5.5)**	91.0 (19.6) **49.7 (3.4)**
Post-Training	108.1 (19.5)* **43.9 (6.6)***	7.4 (4.2) **39.2 (4.2)**	66.6 (18.9) **46.1 (4.5)**	93.5 (20.9) **50.4 (2.1)**
COMBO				
Pre-Training	103.5 (23.4) **44.6 (6.7)**	7.6 (1.5) **37.0 (10.6)**	63.6 (13.5) **46.5 (5.1)**	88.8 (15) **50.5 (3.0)**
Post-Training	104.9 (19.6) **44.2 (6.2)**	8.7 (2.1) **41.0 (5.1)**	64.4 (11.8) **45.8 (4.3)**	89.3 (13.7) **50.8 (1.9)**