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Muscle Deficits in Rheumatoid Arthritis Contribute to Inferior Cortical Bone Structure and Trabecular Bone Mineral Density

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Abstract

Objective—Rheumatoid arthritis (RA) is associated with muscle loss, osteoporosis, and fracture. We examined associations between skeletal muscle mass, strength, and quality and trabecular and cortical bone deficits in patients with RA and healthy controls.

Methods—Participants, ages 18–75 years, completed whole-body DXA and peripheral quantitative CT of the tibia to quantify appendicular lean mass and fat mass indices (ALMI, FMI), muscle density at the lower leg, trabecular bone density, and cortical bone thickness. Age-, sex-, and race-specific Z-Scores were calculated based on distributions in controls. Associations between body composition and pQCT bone outcomes were assessed in RA and controls. Linear regression analyses assessed differences in bone outcomes after considering differences in body mass index (BMI) and body composition.

Results—The sample consisted of 112 RA patients (55 men) and 412 controls (194 men). Compared to controls, RA patients had greater BMI ($p=0.004$), lower ALMI after adjustment for FMI ($p=0.02$), lower muscle strength ($p=0.006$), and lower muscle density ($p<0.0001$). Among RA, ALMI Z-Scores were positively associated with trabecular density [β : 0.29 (0.062, 0.52)]

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Conflicts of Interest

The authors have nothing to disclose.

p=0.01] and cortical thickness [β : 0.32 (0.13,0.53) p=0.002]. Associations were similar in controls. Bone outcomes were inferior in RA patients after adjusting for BMI but similar to controls when adjusting for body composition. Radiographic damage and higher adiponectin levels were independently associated with inferior bone outcomes.

Conclusions—Patients with RA exhibit deficits in cortical bone structure and trabecular density at the tibia and a preserved functional muscle-bone unit. A loss of mechanical loading may contribute to bone deficits.

Keywords

Bone structure; rheumatoid arthritis; body composition; muscle

Introduction

Rheumatoid arthritis (RA) is associated with a greater risk of osteoporotic fractures (1). Patients with RA have deficits in cortical and trabecular bone related to effects of systemic inflammation on endosteal and trabecular bone resorption (2–4). In addition to the direct effects of inflammation on bone remodeling, muscle loss and adverse fat distribution may also contribute to adverse bone outcomes (5–10). However, few studies have evaluated associations between body composition and bone outcomes in RA (11–13), and only one previous study compared these associations to those observed in controls (14).

Research in astronauts has suggested that bone adapts to the mechanical forces placed upon it (15). The theory is termed the functional muscle-bone unit and explains why cortical geometry, bone density, and fracture load are superior among individuals with larger body size (8–10). It has been observed that Olympic fencers have greater thickness of cortical bone and greater trabecular bone mineral density in the leg that undergoes greater mechanical loading and has greater muscle mass (16). Muscle mass and muscle forces are associated with superior bone structure and density as well as lower fracture risk independent of measures of fat (17–20). In contrast, greater visceral and intramuscular fat are associated with adverse bone structure and an increased risk of fracture in the general population (5–7).

Cortical bone structure and trabecular volumetric bone mineral density (vBMD) are commonly evaluated using peripheral quantitative computed tomography (pQCT). pQCT measures of cortical dimensions can predict failure load in the human radius and femoral neck in cadaveric studies (21) and predict incident fractures in cohort studies among older adults (22, 23). We have previously shown that the dimensions of cortical bone are associated with appendicular lean mass, muscle-specific force (muscle strength relative to muscle mass), and muscle density (a correlate of intramuscular fat accumulation) among healthy participants (18). In a study of 50 patients with RA, pQCT measures of vBMD and cortical cross-sectional area were associated with muscle cross-sectional area in women with RA and female controls at the tibia (14). However, in addition to low sample size and inclusion of women only, that study did not examine the impact of other important features of body composition and muscle quality such as total or visceral fat mass, muscle density, and muscle strength - factors that have been associated with muscle outcomes in healthy

controls. (5–7, 24) Previous studies have also been limited in their assessment of other disease characteristics such as physical activity, inflammatory cytokines, radiographic damage, prednisone use, and other phenotypic assessments.

This study aimed to address this knowledge gap by examining bone density and structure and the impact of muscle-bone interactions among RA patients compared to healthy controls. We hypothesized that deficits in muscle mass, quality, and strength would be associated with cortical bone structure and trabecular vBMD in RA and that these associations would be similar to associations observed in healthy controls. We also assessed whether muscle deficits in RA patients could explain a portion of their bone deficits compared to controls.

Methods

Study Sample

Patients with RA, ages 18–75 years, who met 2010 American College of Rheumatology classification criteria, were recruited from the University of Pennsylvania and Philadelphia VA Medical Center Rheumatology practices. Older patients were excluded to avoid confounding by advanced age. Patients with Juvenile Idiopathic Arthritis (or another inflammatory arthritis), active cancer, a history of chronic diseases known to affect bone health (e.g. chronic kidney disease, liver disease, or malabsorption syndromes), or pregnancy were excluded. Muscle outcomes from the pilot study (N=50) have been previously published (25). Patients were excluded if their weight was >300 pounds due to weight limitations of the equipment.

Adult controls, ages 21 to 78 years (239 male, 261 female), were enrolled as healthy reference participants for multiple bone studies at the University of Pennsylvania, as previously described (18). These participants were recruited from Internal Medicine clinics and the surrounding community using flyers and newspaper advertisements. Exclusion criteria included a history of chronic diseases or medications known to affect nutrition or bone health, such as a reported history of diabetes, malabsorption syndromes, chronic kidney disease, liver disease, thyroid disease or malignancy. The bone and body composition results in the controls have been described (18). All study participants (RA and controls) underwent scans in the same laboratory using identical equipment and methods. For each subject, all measurements were performed at the same study visit. The protocol was approved by the Institutional Review Boards at the University of Pennsylvania (Study #813724) and at the Corporal Michael J. Crescenz VA Medical Center (Study #01427). Informed consent was obtained from all participants.

Assessment of Anthropometrics and Race

Weight and height were measured using a digital scale (*Scaltronix, White Plains, NY*) and stadiometer (*Holtain Ltd., Crymych, UK*), respectively. Body Mass Index (BMI) was calculated by dividing weight in kilograms by height in meters-squared. Participants self-identified race according to National Institute of Health categories.

Peripheral Quantitative Computed Tomography (pQCT)

Muscle, fat, and bone measures in the left lower leg were obtained by pQCT (*Stratec XCT2000 12-detector unit, Orthometrix, Inc.*) with a voxel size of 0.4 mm, slice thickness of 2.3 mm, and scan speed of 25 mm/sec. A scout view was obtained to place the reference line at the proximal border of the distal endplate. The bone measurements were obtained at 3% and 38% of tibia length proximal to the reference line. At the 3% metaphyseal site, scans were analyzed for trabecular vBMD (mg/cm^3) with contour mode 3 threshold $169 \text{ mg}/\text{cm}^3$, and peel mode 4 threshold $650 \text{ mg}/\text{cm}^3$ with an additional 10% concentric peel. At the 38% diaphyseal site, scans were analyzed for cortical vBMD (mg/cm^3) using a threshold of $710 \text{ mg}/\text{cm}^3$ to separate bone from soft tissue. For bone outcomes, we used analysis modes based on the study by Ashe, et al. (26). We considered cortical thickness as the primary cortical structure outcome of interest since the study by Ashe et al. demonstrated that cortical thickness was the cortical geometry measure with the greatest correlation with fracture load ($R^2=0.81$, $p<0.001$) and previous studies identified associations with risk of fracture (27). Trabecular vBMD also correlates highly with fracture load ($R^2=0.72$ $P<0.001$) (28, 29).

Calf muscle and subcutaneous fat cross-sectional area (CSA) (mm^2) were assessed 66% proximal to the distal physis (where muscle is prominent) using a threshold of $40 \text{ mg}/\text{cm}^3$ for fat/lean separation and $711 \text{ mg}/\text{cm}^3$ for lean/bone separation. (20, 30). The pQCT measure of muscle density (mg/cm^3) was used as a composite index of intra and extra-myocellular fat content, as previously described (20, 30). Edge-detection and threshold techniques were used to separate tissues (skin, fat, muscle, marrow, and bone) based on attenuation characteristics that are directly related to tissue composition and density (31, 32). Images were filtered prior to being analyzed using contour mode 3 ($-101 \text{ mg}/\text{cm}^3$) to find skin, and peel mode 2 ($40 \text{ mg}/\text{cm}^3$) to separate adipose and muscle/bone, respectively. Images were filtered subsequently with a combination 3×3 , and double 5×5 kernel image filter that clearly defined the edge of the muscle using contour mode 31 ($40 \text{ mg}/\text{cm}^3$). All bone was identified using a threshold of $150 \text{ mg}/\text{cm}^3$ and mathematically removed to generate results for muscle density. In our laboratory, the coefficient of variation (CV) for short-term precision has ranged from 0.5 to 1.6% for pQCT outcomes.

Whole-body Dual-Energy Absorptiometry (DXA)

Subjects underwent whole-body DXA assessment using a Hologic densitometer (Delphi Systems, *Hologic, Inc., Bedford, MA*) to measure appendicular lean mass, as well as total and regional fat mass. The in vitro CV for Hologic measurement of lean mass was less than 0.6% and the in vivo CV in adults was less than 1% (33). We utilized a previously validated method to quantify visceral adipose tissue (VAT) area (34). The CV for VAT was 5.3%.

Dynamometric Measurement of Muscle Strength

Muscle strength was assessed using Biodex Multi-Joint System 3 Pro Dynamometer (*Biodex Medical Systems, Inc, Shirley, NY*). High intra-rater (0.97 to 0.99) and inter-rater (0.93 to 0.96) intra-class correlation coefficients have been reported (35). We reported strength as peak isokinetic torque (ft-lbs) in dorsiflexion (with the foot placed in 20 degrees of plantarflexion) as previously described (36).

Physical Activity Questionnaire

Physical activity was assessed using a detailed questionnaire developed for the Multi-Ethnic Study of Atherosclerosis (MESA) (37). We used a definition of intentional exercise (the sum of walking for exercise, sports/dancing, and conditioning MET-hours/week) that has been previously defined (18). The total number of reported sedentary hours per week was also recorded.

Disease Measures and Inflammatory Markers

Clinical laboratory assays [Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP)] were performed using standard methods. ESR was performed using the Westergren method. CRP levels were measured using a Fixed Point Immuno Rate Assay. Medication use was determined by self-report and confirmed in the medical record. Individuals on corticosteroids were not excluded in order to study their potential impact on bone outcomes. Disease activity and disability were measured in a standard fashion using the Disease Activity Score 28 (DAS28) with CRP and the Health Assessment Questionnaire (HAQ) (38). Cytokine assays were performed using a V-Plex Plus Proinflammatory Panel 1 kit from *Meso Scale Discovery*. 25(OH) Vitamin D was measured using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS). Adiponectin was measured by ELISA kit from *R&D Systems* and leptin was measured by using a kit from *Meso Scale Discovery*. Sclerostin was measured with ELISA kit from *ALPCO Diagnostics*. Radiographic joint damage was measured in the hands and feet using the van der Heijde-Sharp (vdHS) scoring system. Seventeen subjects failed to return to complete x-rays at baseline.

Statistical Analysis

Multiple imputation for pQCT outcomes and vdHS scores was performed to account for missing data. pQCT values were imputed for nine subjects who were not able to complete the scan due to discomfort or excess calf size. The imputed analysis was considered more conservative, but results were similar with exclusion of patients with missing data. pQCT outcomes, and BMI values were converted to age, sex, and race-specific standard deviation scores (Z-Scores) based on distributions among the control population using LMS (*Lambda*, *Mu*, *Sigma*) curves as described previously (25). The use of Z-Scores helps to account for the effects of age, sex, and race, as well as the non-linearity, heteroskedasticity, and skew noted in these outcomes (25, 39–41). A Z-Score below zero suggests a below average value for that outcome. ALMI Z-Scores were assessed between RA and controls before and after adjustment for FMI Z-Scores. As previously shown, ALMI and FMI Z-Scores are correlated and greater adiposity can therefore obscure a relative loss of muscle mass (39, 42).

Differences in the primary bone structural outcomes of trabecular vBMD and cortical thickness Z-Scores between RA and controls were evaluated before and after adjustment for BMI Z-Scores (to determine if bone outcomes are adapted to BMI) using multivariable linear regression. Differences in bone outcomes between RA and controls were subsequently assessed before and after adjustment for ALMI Z-Score, FMI Z-Score and muscle density Z-Score in sequential models. Disease characteristics independently associated with pQCT bone outcomes were assessed in multivariable models. The study was designed to have approximately 80% power to detect small to moderate effect sizes between groups ($d=0.32$)

and to detect a coefficient of determination (r^2) of 0.078 or greater among RA participants. Analyses were performed with STATA 14.1 (*StataCorp, LP, College Station, TX*).

Results

The characteristics of the study population are summarized in Table 1. Briefly, a total of 112 eligible RA participants and 412 controls completed study procedures and were included in the analysis. RA participants were generally older but were otherwise similar in terms of demographics. RA participants had a median disease duration of 7.6 years and low disease activity on average. Most patients previously received methotrexate, and approximately half received biologics previously. Forty-five percent of subjects were currently receiving prednisone.

RA participants had greater BMI than the reference population and were more likely to be obese. RA patients were observed to have greater FMI Z-Scores and greater VAT area (Table 2). Despite higher FMI Z-Scores, RA patients had similar ALMI Z-Scores, and significantly lower ALMI Z-Scores when adjusting for the greater FMI Z-Score [β : -0.21 (-0.39, -0.035) $p=0.02$]. RA had significantly lower muscle CSA on pQCT (Table 2). Patients with RA had lower muscle density Z-Scores compared to controls. Muscle strength Z-Scores were also lower in RA and this difference persisted with adjustment for ALMI and FMI Z-Score [β : -0.21 (-0.41, -0.011) $p=0.04$], suggesting low muscle-specific force.

Trabecular vBMD Z-scores and cortical thickness Z-Scores were not lower than controls in unadjusted analyses (Table 2). In regression models adjusting for the greater BMI Z-Score observed in RA, there were significant, albeit modest, deficits among RA participants compared to controls for cortical thickness [β : -0.35 (-0.61, -0.097) $p=0.03$] (Figure 1). Patients with RA also tended to have lower trabecular vBMD Z-Scores with adjustment for BMI Z-Score [β : -0.26 (-0.52, 0.004) $p=0.054$].

Assessment of the Functional Muscle-Bone Unit in RA and Controls

Amongst RA and controls, greater ALMI Z-Score was strongly correlated with greater trabecular vBMD ($R=0.32$, $p<0.001$) and cortical thickness Z-Scores ($R=0.36$, $p<0.001$). Independent associations between ALMI Z-Score, FMI Z-Score, and muscle density Z-Score and bone outcomes were similar in RA compared to controls in multivariable models (Figure 1, Table 3) (no significant interaction; all $p>0.28$). Adjustment for differences in ALMI, FMI, and muscle density Z-Scores attenuated bone deficits observed for RA (Figure 2).

Among RA patients, ALMI Z-Score was positively associated with trabecular vBMD Z-Scores and cortical thickness Z-Scores (Table 3). In addition, patients with RA who had a low lean mass for their age (ALMI Z-Score -1, 15.9th percentile) had substantially lower cortical thickness Z-Scores [β : -0.58 (-1.02, -0.14) $p=0.01$] and trabecular vBMD Z-Scores [β : -0.79 (-1.28, -0.29) $p=0.002$]. Greater ALMI Z-Scores were associated with greater periosteal circumference Z-Scores [β : 0.32 (0.091, 0.56) $p=0.007$], but were not associated with endosteal circumference Z-Scores [β : -0.041 (-0.20, 0.28) $p=0.73$]. Muscle density and muscle strength Z-Scores were not independently associated with bone outcomes.

independent of ALMI Z-Score amongst RA (Table 3). In similar models, greater muscle density Z-score was associated with smaller endosteal circumference [β : -0.23 (-0.41 , 0.051) $p=0.01$] but was not associated with periosteal circumference [β : -0.14 (-0.32 , 0.040) $p=0.12$]. Associations were similar in sensitivity analyses excluding patients who ever used bisphosphonates.

Impact of RA Disease Characteristics

In regression models, factors associated with lower trabecular vBMD Z-Scores included disease duration, ever and current prednisone use, greater joint damage, greater adiponectin levels, and lower leptin levels. Factors associated with lower cortical thickness Z-Scores included greater joint damage, greater disease duration, and greater adiponectin levels.

In multivariable models including age, black race, ALMI, FMI, and muscle density Z-Scores, males had significantly lower trabecular vBMD Z-Scores compared to women [β : -0.42 (-0.81 , -0.034) $p=0.03$]. In multivariable models, higher $\ln(\text{vdHS})$ scores were associated with lower trabecular vBMD Z-Score [β : -0.23 (-0.35 , -0.11) $p<0.001$] independent of body composition. Higher adiponectin levels were also associated independently with lower trabecular vBMD [β : -0.039 (-0.075 , -0.003) $p=0.04$] and cortical thickness [β : -0.033 (-0.066 , 0.000) $p=0.05$].

Other disease characteristics were not significantly associated with bone outcomes independent of body composition including disease activity [DAS28(CRP)], inflammatory cytokines (IL-6, TNF- α), prednisone use (ever, current, or total years of use), other medication use, physical activity, smoking, 25OH vitamin D levels, sclerostin levels and RA disease duration in these models (all $p>0.05$).

Discussion

This study demonstrated that patients with RA have deficits in muscle mass, quality, and strength as well as modest deficits in trabecular vBMD and cortical structure as measured by pQCT compared to what would be expected for their BMI. In this study, the associations between body composition and bone outcomes were similar in RA and controls, suggesting that the functional muscle-bone unit is preserved in this group. Overall, these observations support the hypothesis that deficits in cortical bone structure and trabecular vBMD in this group may be explained, in part, by a loss of skeletal muscle mass, muscle quality, and reduced mechanical loading to bone.

The bone deficits observed among RA participants in this study using pQCT were modest, on average, with a “small” effect size between groups (0.26 and 0.35 for trabecular vBMD and cortical thickness, respectively). In comparison, a study of 50 women with RA from Switzerland reported moderate effect sizes between RA and controls at the tibia (0.65 and 0.52 for trabecular vBMD and cortical thickness, respectively) (14). More modest deficits observed in the current study might suggest an impact of secular trends in disease management. For example, this cohort had a high frequency of biologic use and low disease activity. Alternatively, these differences may reflect differences in disease populations, selection of participants, or methods utilized to quantify deficits.

There has been recent interest in the impact of muscle loss on bone loss among patients with RA (12, 13). We are aware of only one previous study characterizing associations between muscle area and cortical dimensions in women with RA using pQCT (14). The current study is the largest study to evaluate the functional muscle-bone unit in RA compared to a large sample of well-characterized controls and the first to include men. Furthermore, the current study incorporated independent assessment of the effect of total adiposity, intramuscular fat accumulation and resulting low muscle density, as well as muscle strength. These factors have been described as important mediators of adverse bone outcomes in the general population. In this study, appendicular lean mass was the most important predictor of cortical bone structure and trabecular vBMD in the tibia among patients with RA. Greater lean mass was associated with larger periosteal circumference, supporting the hypothesis that greater lean mass promotes larger bone size through periosteal apposition (43, 44).

Greater muscle mass and muscle forces are likely to play an important role in promoting superior cortical bone structure and trabecular vBMD. Though the primary mediators of the muscle-bone interaction remain poorly understood, several potential mechanisms have been described. Mechanical loading to bone has been shown to inhibit osteoclast differentiation and activity to promote bone formation (45). Mechanical stimulation of bone may inhibit osteoclasts through alterations in canalicular fluid flow within the bone and resulting stimulation of mechanoreceptors on osteocytes (46). This stimulation of osteocytes may down-regulate important mediators such as sclerostin, in order to promote new bone formation.

Our study observed strong and comparable associations between skeletal muscle mass and bone outcomes in both RA and controls. Fat mass was not associated with bone outcomes in either RA or controls, confirming previous literature suggesting that the beneficial effect of greater weight on bone structure is mediated through greater lean mass, and not greater adiposity (8–10, 24). Thus weight gain in the fat compartment would be ill advised in attempts to promote superior bone in RA. While measures of disease activity and systemic inflammation were not associated with bone outcomes in this study, the study demonstrated associations between radiographic joint damage and trabecular vBMD independent of muscle mass. This observation confirms that the chronic systemic inflammatory disease independently contributes to bone loss (4).

We previously demonstrated associations between adiponectin and evidence of cachexia in RA (40). The novel associations between adiponectin and bone outcomes observed in this RA cohort were independent of body composition. Since adiponectin has been described as a marker of cachexia and frailty in RA and other populations, high adiponectin levels may be associated with bone outcomes by identifying those with weight loss and frailty. Indeed, associations between adiponectin and bone outcomes were partially attenuated with adjustment for skeletal muscle mass in this study. Studies in other populations have demonstrated associations between adiponectin and bone and fracture outcomes (47, 48).

This study observed deficits in muscle mass, muscle density, and muscle-specific force among individuals with RA compared to a healthy control population and confirms previous studies demonstrating altered body composition among patients with RA. This is the largest

study to describe low muscle density and low muscle-specific force among patients with RA compared to a control population suggesting poor muscle quality in addition to deficits in muscle mass (25, 49, 50).

Limitations of the current study include the cross-sectional design, which does not allow for a clear description of the temporal changes due to the disease. However, the observation of similar cross-sectional associations in RA and controls is the critical observation here that argues against reverse causality. Longitudinal studies may help clarify these questions and are a logical next step. The relatively modest bone deficits observed in this cohort may not be generalizable to cohorts or individuals severely affected by the disease. However, the modest deficits observed here are informative and may reflect meaningful improvements in the management of the disease in recent years. Missing pQCT data due to the patient's inability to perform the test could have resulted in selection bias. However missing data was uncommon and use of multiple imputation limited this potential bias. Strengths of the study include the comparison of RA patients to a large control population across a wide age range using robust methods to quantify deficits in muscle and bone.

In conclusion, this study shows that patients with RA have poorly adapted cortical bone structure and trabecular vBMD for their BMI. Deficits in muscle mass, muscle density, and muscle-specific force are observed in RA and may contribute to bone deficits through a loss of mechanical loading. Altered body composition and frailty are under-recognized risk factors for maladapted bone in RA and may affect the risk of fracture.

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Figure 1.

Associations between appendicular lean mass index Z-Scores and (a) cortical thickness Z-Scores and (b) trabecular vBMD Z-Scores among RA and controls.

Figure 2.

Differences in trabecular vBMD and cortical thickness between RA and controls (presented as a regression coefficient and 95% confidence) with adjustment for BMI and after subsequent adjustment for differences in body composition.

Abbreviations: BMI= Body Mass Index; ALMI= Appendicular Lean Mass Index; FMI= Fat Mass Index.

Table 1

Characteristics of study participants.

	Rheumatoid Arthritis	Healthy Controls	P
N	112	412	--
Age (yrs)	55.9 (12.6)	48.0 (16.0)	<0.0001
Female, N (%)	57 (51%)	218 (52%)	0.70
White, N (%)	66 (59%)	241 (59%)	0.93
Black, N (%)	37 (33%)	171 (42%)	0.10
Body Mass Index, (kg/m²)	28.7 (7.2)	26.0 (5.2)	<0.001
Obese, N (%)	41 (37%)	75 (18%)	<0.001
25(OH) Vitamin D, ng/mL	29.1 (14.0)	24.7 (12.0)	0.001
<u>RA Disease Characteristics</u>			
DAS28 (CRP)	4.07 (1.27)	--	
HAQ Score (0–3.0)	0.79 (0.63)	--	
ACPA Positive , N (%)	92 (82%)	--	
vdHS Score	13.5 (3, 56.5)	--	
Disease Duration, yrs	7.6 (2.6, 17.6)	--	
Current Methotrexate, N (%)	75 (67%)	--	
Current Biologic Therapy, N (%)	57 (51%)	--	
Current Prednisone, N (%)	50 (45%)	--	
Ever Methotrexate, N (%)	95 (87%)	--	
Ever Biologic Therapy, N (%)	74 (66%)	--	
Ever Prednisone, N (%)	87 (78%)	--	
<u>Current Bisphosphonate</u>	<u>8 (7%)</u>	--	
<u>Ever Bisphosphonate</u>	<u>18 (16%)</u>	--	

Results displayed as Mean(SD), Median (IQR) for skewed data, or N (%) for dichotomous data.

Abbreviations: RA= Rheumatoid Arthritis; DAS28(CRP)= Disease Activity Score of 28 joints including C-Reactive Protein; HAQ= Health Assessment Questionnaire; ACPA= Anti-Citrullinated Peptide Antibody;

Table 2

Unadjusted comparison of body composition, bone, and physical activity between RA and controls.

	Rheumatoid Arthritis (N=112)	Healthy Controls (N=412)	P
BMI Z-Score	0.39 (1.43)	-0.067 (0.95)	<0.001
<u>Fat Outcomes</u>			
FMI Z-Score	0.39 (1.25)	-0.010 (0.99)	<0.001
Visceral Fat Area (cm²)	134.3 (73.1)	92.9 (61.1)	<0.001
<u>Physical Activity</u>			
Intentional Exercise (MET-hrs/wk)	15.9 (0, 46.7)	26.8 (8.9, 67.9)	<0.001
Sedentary Time (hrs/wk)	20.5 (10.5, 32.7)	10.0 (4.5, 17.5)	<0.001
<u>Muscle Outcomes</u>			
Calf Muscle CSA Z-score	-0.41 (1.34)	-0.020 (1.02)	0.001
ALMI Z-Score	0.025 (1.21)	-0.014 (1.00)	0.72
Muscle Density Z-score	-0.71 (1.16)	0.062 (1.04)	<0.001
Muscle Strength Z-Scores	-0.26 (1.09)	0.004 (0.90)	0.01
<u>Bone Outcomes</u>			
Cortical Thickness Z-Score	-0.18 (0.95)	-0.045 (0.99)	0.21
Trabecular vBMD Z-Score	-0.071 (1.09)	-0.013 (0.98)	0.59
Endosteal Circumference Z-Score	0.33 (1.01)	0.10 (0.94)	0.03
Periosteal Circumference Z-Score	0.20 (1.01)	0.033 (0.80)	0.09

Abbreviations: RA= Rheumatoid Arthritis; pQCT= Peripheral Quantitative Computed Tomography; CSA= Cross-sectional area; BMI= Body Mass Index; ALMI= Appendicular Lean Mass Index; MET=Metabolic Equivalent of a Task; FMI= Fat Mass Index; vBMD= volumetric Bone Mineral Density

Table 3

Multivariable linear regression models demonstrating independent relationships between body composition and bone Z-Scores among patients with RA and controls.

	Trabecular vBMD Z-Score		Cortical Thickness Z- Score [†]	
	Controls	RA	Controls	RA
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
ALMI Z-Score	0.26 *** (0.15, 0.37)	0.29 * (0.062, 0.52)	0.37 *** (0.26, 0.48)	0.33 ** (0.13, 0.53)
FMI Z-Score	0.071 (-0.044, 0.18)	0.11 (-0.11, 0.34)	-0.006 (-0.12, 0.11)	-0.068 (-0.27, 0.13)
Muscle Density Z-Score	0.11 * (0.020, 0.21)	0.072 (-0.10, 0.25)	0.094 * (0.002, 0.19)	0.11 (-0.049, 0.28)

*
p<0.05

**
p<0.01

p<0.001

[†] Also adjusted for tibia length Z-Score

Abbreviations: vBMD= volumetric Bone Mineral Density; RA= Rheumatoid Arthritis; ALMI= Appendicular Lean Mass Index; FMI= Fat Mass Index

Table 4

Age-, sex-, and black race-adjusted associations between individual RA factors and bone outcomes among patients with RA. Each variable represents a separate multivariable regression model.

	Trabecular vBMD Z-Score		Cortical Thickness Z-Score	
	β (95% CI)	p	β (95% CI)	p
DAS28(CRP)	−0.098 (−0.26, 0.064)	0.23	−0.018 (−0.17, 0.13)	0.81
IL-6 Level (pg/mL)	−0.006 (−0.047, 0.036)	0.80	−0.001 (−0.038, 0.037)	0.97
TNF-alpha Level (pg/mL)	−0.008 (−0.020, 0.0049)	0.23	−0.002 (−0.013, 0.010)	0.74
Ln(vdHS)	−0.28 (−0.40, −0.17)	<0.001	−0.17 (−0.29, −0.049)	0.006
Disease Duration (per 10 yrs)	−0.19 (−0.37, 0.007)	0.04	−0.022 (−0.038, −0.005)	0.01
Current Prednisone	−0.46 (−0.85, −0.065)	0.02	−0.078 (−0.44, 0.29)	0.67
Ever Prednisone Use	−0.59 (−1.06, −0.11)	0.02	−0.26 (−0.69, 0.18)	0.25
Current Smoking	−0.34 (−0.81, 0.12)	0.14	−0.14 (−0.57, 0.28)	0.50
25(OH) Vitamin D (ng/mL)	0.006 (−0.009, 0.021)	0.41	0.005 (−0.009, 0.018)	0.50
Adiponectin (ug/mL)	−0.061 (−0.096, −0.027)	0.001	−0.053 (−0.085, −0.021)	0.001
Leptin (ug/mL)	0.007 (0.001, 0.013)	0.02	0.005 (−0.000, 0.12)	0.06

Associations adjusted for age, sex, and black race.

Abbreviations: vBMD= volumetric Bone Mineral Density; DAS28(CRP)= Disease Activity Score in 28 Joints with C-Reactive Protein; vdHS= van der Heide-Score; IL-6= Interleukin-6; TNF= Tumor Necrosis Factor