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Association of High Anti-Cyclic Citrullinated Peptide Seropositivity and Lean Mass Index with Low Bone Mineral Density in Rheumatoid Arthritis

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Abstract

Objective—Osteoporotic fractures are associated with high morbidity and mortality. Persons with rheumatoid arthritis (RA) have twice the risk of osteoporosis-related fracture than age-matched controls, the causes for which remain unknown. We investigated contributions of RA characteristics, medication use, and body composition to low bone mineral density (BMD) in patients with RA.

Methods—Data were from the Arthritis, Body Composition, and Disability Study (n=138; 82 women, 56 men). Demographic, clinical, laboratory and functional variables were collected at study visits. Body composition (fat, lean muscle and BMD) was measured by dual x-ray absorptiometry. Linear regression analyses evaluated the association between predictors and femoral neck BMD.

Results—Average disease duration was 19 years, 70% of patients were rheumatoid factor positive and 55% were high-positive anti-cyclic citrullinated peptide (CCP). Age and high anti-CCP positivity were negatively associated with BMD after controlling for other variables ($\beta = -0.003$ and -0.055, respectively, $p<0.05$). Appendicular lean mass index (ALMI) was positively associated with BMD ($\beta=0.053$, $p<0.0001$). In high-positive anti-CCP participants, increasing anti-CCP levels were associated with a negative linear trend in BMD ($\beta=-0.011$, $p=0.026$).

Conclusion—High anti-CCP positivity and ALMI were strongly associated with BMD in patients with RA. The linear relationship of anti-CCP levels with lower BMD supports the

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hypothesis that processes specific to RA negatively impact BMD. In contrast, ALMI was positively associated with BMD, emphasizing the importance of this potentially modifiable risk factor. Our findings highlight the complicated interplay of RA disease-specific and functional factors and their impact on bone mass.

Introduction

Osteoporotic fractures are associated with increased morbidity and mortality (1). As a common secondary cause for low bone mineral density (BMD), rheumatoid arthritis (RA) is a major contributor to osteoporotic fractures. In patients with RA, the relative risks (RR) of hip fracture and spinal compression fracture are 2.0- and 2.4-fold greater, respectively, compared to age- and sex-matched controls (2). RA is an independent risk factor for fracture in the Fracture Risk Assessment Tool (FRAX) (3). Fractures in RA patients may also predict increased mortality (4,5), underscoring the importance of identifying and mitigating risk factors that contribute to the lower BMD and skeletal fragility in patients with RA. Unfortunately, BMD testing by dual x-ray absorptiometry (DXA) is often overlooked in patients with RA (6,7). Without such testing, patients at heightened fracture risk may not be identified and treated, leading to underutilization of potentially life-saving interventions (8).

The heightened risk of skeletal fragility in RA is thought to be due to a combination of the primary effects of the disease, the medications used to treat it, notably glucocorticoids (GCs), and reduced physical activity (2,9). It is not known, however, which characteristics of RA or its treatments have the greatest impact on the BMD and fracture risk. The American College of Rheumatology (ACR) has published guidelines on the diagnosis and treatment of glucocorticoid-induced osteoporosis, but has no recommendations on prevention or treatment of osteoporosis in RA (10). A key first step to improving bone health interventions in patients with RA is understanding which patients are at highest risk of developing low BMD and osteoporotic fractures. Investigators have used observational data to determine which patients with RA are at increased risk for low BMD (9,11,12) or fracture (2,13). Common factors associated with low BMD or fracture in these studies include age, low BMI, GC use and disease duration. Prior studies have been key to improving the understanding of risk factors for low BMD in RA, but studies that include the full range of clinical and disease-related factors that may be relevant, such as medication use, disease activity, RF or Anti-CCP antibody status or body composition are still needed.

Body composition is known to influence BMD (14). In the general population, greater adiposity as measured by body mass index (BMI) and lean muscle mass are both associated with increased BMD (14,15). Individuals with RA, particularly men, are at risk for altered body composition with higher rates of sarcopenia and increased fat mass compared to the general population (16–18). This altered body composition, specifically low lean muscle mass, may have an important effect on bone density in RA patients.

Using a well-characterized cohort of community-dwelling patients with RA, we evaluated the associations of body composition, clinical parameters, and laboratory characteristics with femoral neck BMD in individuals with RA. Understanding the characteristics predisposing to low BMD is an important step towards understanding those who are at

highest risk for fracture and may elucidate pathways for intervention and ultimately improve fracture-related morbidity and mortality in patients with RA.

Patients and Methods

Subjects

Individuals in this study were participants in the Arthritis, Body Composition, and Disability (ABCD) study, a cohort developed at the University of California, San Francisco (UCSF) to study relationships between body composition and physical function in patients with RA and systemic lupus erythematosus (SLE). Data were collected between 2007–2009. Details of this cohort have been previously reported by Katz et al. (17). For this secondary analysis of the pre-existing dataset, we evaluated only those patients with a diagnosis of RA. All participants had rheumatologist-diagnosed RA. Exclusion criteria were non-English-speaking, age <18 years, current pregnancy, and daily oral prednisone dose ≥50 mg. The exclusionary dose of prednisone was set at 50 mg to exclude those with severe, actively flaring SLE.

Of 242 eligible individuals, 97 (40%) declined participation, primarily because of transportation (n=36) and scheduling difficulties (n=38); 145 individuals completed the study visit. Seven participants were excluded from the analysis because they did not complete the body composition assessment (including DXA BMD measurement). Of the remaining 138 participants, 82 (59%) were women and 56 (41%) were men. The study was approved by the UCSF Committee on Human Research, and all participants provided written informed consent.

Variables

Bone mineral density (BMD)—BMD was assessed in the UCSF Clinical Research Center using the Lunar Prodigy DXA system (software version 9.3). DXA has been validated as a method of assessing BMD as well as body composition and has good reproducibility (19,20). The root-mean-square coefficient of variation for the Lunar Prodigy DXA system is 0.77% for BMD, 2.98% for total fat and 1.42% for lean mass (21). Our primary outcome measurement was BMD at the femoral neck (g/cm^2). We created a dichotomous variable (low BMD) that identified anyone with a T-score ≤−1 if they were 50 years of age or older and Z-score ≤−1 for those younger than 50. As menopausal status was not collected, we used age 50 as the cutoff for using T- or Z-score.

Body composition—Weight was measured with subjects wearing light indoor clothing and no shoes. Height was measured with a wall-mounted stadiometer. BMI was calculated as weight (kg) divided by height (m^2). DXA has previously been used to study body composition in RA (17,22,23), and yields data on total percent body fat as well as total and segmented fat and lean mass. Obesity was defined using a method that linked percent fat from DXA to the National Institutes of Health BMI obesity criterion (BMI ≥30 kg/m^2) by sex, age, and race (24). This definition has been previously used in RA and is thought to represent a conservative measure of obesity (18). Fat mass (FMI) and appendicular lean mass (ALMI) indices were calculated as kg/m^2.

Functional measurements—Lower extremity muscle strength was assessed using a Biodex® unit to measure peak isokinetic torque of knee flexion as previously described (25). Participants completed three trials, and the average maximal strength was calculated. Physical activity was assessed by self-report with the long form of the International Physical Activity Questionnaire (IPAQ) (26). The IPAQ has been used and validated in a number of populations (27,28). Individuals who self-reported fewer than 600 metabolic equivalent (MET) minutes per week were classified as having low physical activity (26).

RA Disease Characteristics and Medications—RA disease duration (in years) and the Rheumatoid Arthritis Disease Activity Index (RADAI) were obtained by self-report (29). Blood samples were collected during the study visit. High sensitivity C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) levels were measured at a single commercial laboratory. RF was determined to be positive if >10 IU/mL. We used the European League Against Rheumatism (EULAR)/ACR 2010 classification criteria definition of high-positive anti-CCP which is defined as three times the upper limit of normal (30). Using this criterion, the cutoff for high anti-CCP positivity in our study was 60 units. In order to minimize the heterogeneity of the high anti-CCP group, participants who fell within the low-to-intermediate anti-CCP positive group (n=10) were included with those who were anti-CCP negative. Almost 80% of study participants were concordant in their RF and anti-CCP status. To avoid multi-collinearity, we chose to use anti-CCP status in our regression analyses because it had a stronger association with BMD.

Use and dosage of prednisone and tumor necrosis factor (TNF) inhibitors were queried. Osteoporosis medication, calcium and vitamin D use were determined by open-ended medication report. Information on past bisphosphonate use was not collected.

Other—Age, race, and smoking status were self-reported.

Statistical analyses

Chi-square and t-test analyses were used to detect sex differences in participant characteristics. Linear regression analyses were used to determine univariable associations between predictors and femoral neck BMD. To identify independent predictors of BMD, we performed multivariable linear regression analyses that included variables significant in the univariable analyses of the total sample at $p<0.10$. Prednisone dose was included in the adjusted model, despite having not achieving significance at the $p<0.10$, given the known deleterious effects of prednisone on BMD. Osteoporosis medications were not included in the multivariable analyses due to the inverse association with BMD suggesting indication bias. Because of the significant differences in body composition previously noted between men and women in this dataset (17,18), univariable and multivariable analyses were performed on the entire study population and then stratified by sex.

Secondary analyses—We performed a secondary analysis to further investigate the association of anti-CCP level and BMD using a continuous variable based on 20-unit increments anti-CCP level rather than a dichotomous variable. Multivariable linear

regression was used to determine independent associations with BMD in anti-CCP positive patients. Because of the relatively small sample, we did not stratify this analysis by sex.

Additional sensitivity analyses were performed to include study subjects that did not participate in the knee flexion Biodex® measurement (n=22) to determine if missing observations influenced our results. We included only subjects whose reasons for not participating were pain, frailty or recent joint replacement (n=11), and assigned the lowest sex-specific measurement to them (25). The multivariable analyses described above were then performed on the entire study population and also stratified by sex. We also performed the multivariable analyses without using the knee flexion variable. Lastly, as osteoporosis medication use may confound the relationship between our predictors and BMD, we performed final sensitivity analysis evaluating only those patients who did not report osteoporosis medication use (n=80). Statistical analyses were conducted using Stata, version 13.1 (StataCorp, College Station, TX).

Results

The study cohort was comprised of 138 participants; 82 were female (59%). The average age was 58±10.8 years and 78% were white (Table 1). Subjects had mean RA disease duration of 19±10.9 years, 70% were RF positive and 55% were high anti-CCP positive. 5.8% of study participants reported being current smokers. One third of the participants were taking prednisone at the time of the study, with an average dose of 7.1±6.1 mg/day among users. Approximately half (52%) had low femoral neck BMD (as defined above) and 27% of study participants reported taking osteoporosis medications. One individual self-reported estrogen use but was also taking bisphosphonates. No subjects reported use of parathyroid hormone (1–34), raloxifene or calcitonin.

Age, race and disease characteristics were similar between men and women except women had significantly longer disease duration (20.9 vs. 16.1 years, p=0.010) (Table 1). Medication use was also similar between men and women with men having a trend towards higher use of TNF inhibitors (55% vs. 39%, p=0.059). Sex differences in body composition were found. Expected differences included statistically significantly higher ALMI in men compared to women (6.9 vs. 6.1, p<0.0001) as well as higher average femoral neck BMD in men (0.911 in men vs. 0.863 in women, p=0.041). Men also had higher BMI (28.6 vs. 26.2 in women, p=0.021). Men had higher rates of obesity as defined by DXA total fat (80% of men were obese vs. 44% of women, p<0.0001) and higher rates of self-reported low physical activity (43% for men vs. 27% for women, p=0.050). Although men had greater appendicular lean mass, knee flexion strength was similar between male and female subjects.

Univariable associations with BMD showed that age, RF positivity, high anti-CCP positivity and longer disease duration were negatively associated with BMD (all p<0.05; Table 2). Osteoporosis medication use also had a strong negative association with BMD (β= −0.100, p<0.0001). Male sex, BMI, increased knee flexion strength, ALMI and FMI were positively associated with BMD (all p<0.05 except FMI p<0.1).

Sex differences were noted in the univariable associations with BMD (Table 2). ALMI, osteoporosis medication use, and knee flexion strength remained highly statistically significant for both men and women ($p<0.05$). High anti-CCP positivity was highly statistically significant in women and on the margin of significance in men ($p=0.020$ and 0.052, respectively). Additionally, within females, obesity based on DXA total fat had a positive association with BMD, and RF positivity and oral steroid dose had negative associations with BMD ($p<0.1$ except RF $p<0.05$). RF positivity was not associated with BMD in males, nor was BMI or FMI. Disease activity as measured by RADAI did not have a significant association with femoral neck BMD in this study.

Age, sex, high anti-CCP positivity, disease duration, FMI, ALMI and knee flexion each met the pre-specified inclusion criterion from univariable analyses and were included in the multivariable linear regression analyses. Additionally, we included prednisone dose, despite it not reaching statistical significance in the univariable analyses, because of its known impact on BMD. Osteoporosis medications were not used in the multivariable model as their strong negative association with BMD likely represented confounding by indication. Greater age ($\beta=-0.003$, $p=0.009$), high-positive anti-CCP ($\beta=-0.054$, $p=0.016$), and lower ALMI ($\beta=-0.053$, $p<0.0001$), were significantly and independently associated with lower BMD (Table 3).

Results from sex-specific multivariable linear regressions analyses are shown in Table 4. Age was no longer statistically significantly associated with BMD among females, although it maintained a weak negative trend. High anti-CCP positivity maintained a strong negative association with BMD ($\beta=-0.055$, $p=0.051$). In females, ALMI remained statistically significant with a positive association with BMD ($\beta=0.037$, $p=0.048$). In order to improve power of our estimation, due to the low number of participants in the male subgroup (n=44), FMI and prednisone dose (both $p>0.5$ in univariable model stratified by male sex) were excluded from the multivariable model. For males, greater age and lower ALMI maintained significant associations with BMD ($\beta=-0.004$, $p=0.025$ and $\beta=0.060$, $p=0.001$, respectively). High-positive anti-CCP maintained a point estimate similar to that seen in females ($\beta=-0.057$), but was not statistically significantly associated with femoral neck BMD ($p=0.189$).

The multivariable sensitivity analysis including only high-positive anti-CCP participants (n=61) demonstrated that for every 20-unit increase in anti-CCP level, BMD decreased on average by 0.011 g/cm^2 ($p=0.026$) (Table 5). Additionally, ALMI maintained a strong, positive association with BMD ($\beta=0.037$, $p=0.018$). Age, male sex, disease duration and knee flexion strength were not statistically significant in this model.

The sensitivity analysis adding 11 participants without strength measurements who were not included in the primary analysis found no substantive changes in the β-coefficients. Removing the knee flexion variable from our multivariable model increased the number of subjects in the model (n=134), but did not result in substantial changes in the β-coefficients. Lastly, we found similar results to our primary multivariable model when evaluating only those patients who did not report taking osteoporosis medications (n=80). High anti-CCP positivity and ALMI retained their strong-negative and strong-positive associations with BMD ($\beta=-0.060$, $p=0.034$ and $\beta=0.053$, $p=0.001$, respectively).

Discussion

This study evaluated the associations of laboratory and clinical features of RA, body composition, and functional measures on femoral neck BMD in individuals with RA and found significant univariable effects of each on BMD. We found a strong independent association between high anti-CCP positivity and decreased femoral neck BMD in patients with RA. Additionally, we found a level-dependent negative effect of anti-CCP on femoral neck BMD in patients with anti-CCP levels >60 units.

Anti-CCP positivity reflects the presence of anti-citrullinated protein antibodies (ACPAs). ACPA-positive and ACPA-negative RA are distinct entities that differ in their genetic risk profiles, known environmental triggers, and clinical course (31). The basis for lower BMD in ACPA-positive disease is unknown, but anti-CCP positivity has been linked to low BMD even in early RA, suggesting that systemic bone loss is an intrinsic characteristic of ACPA-positive RA (32). ACPAs can be detected years before the onset of clinical arthritis in RA, and certain ACPAs can induce the differentiation and activation of osteoclasts *in vitro* (33,34). It has been postulated that these effects of ACPAs contribute to osteoclast-mediated erosion of peri-articular bone in RA. The observed link between anti-CCP positivity and low BMD also raises the possibility that ACPA-induced activation of osteoclasts *in vivo* may promote systemic bone resorption leading to low BMD in anti-CCP positive RA patients (35). Further support for the hypothesis that ACPAs may play a direct role in lowering BMD is our finding of a level-dependent negative effect of anti-CCP on femoral neck BMD in anti-CCP positive patients. This suggests that perhaps higher levels of ACPAs, as measured by anti-CCP level, promote greater systemic bone resorption. A similar finding was described in a study by Orsolini et al., who found a negative correlation between tertiles of anti-CCP level and BMD at multiple locations in patients with established RA (35).

We found a strong positive association between ALMI and femoral neck BMD, a finding well supported by the literature both in RA and the general population (36–41). Mechanical loading, through muscular contraction and activity, is thought to have a positive influence on bone mass. Studies have shown that there is a positive association between knee flexion strength and spine and femoral neck BMD (42,43). We did not find a strong association between knee flexion strength and BMD in our multivariable model, but it is possible that our sample size limited our ability to detect a significant effect.

Our study also evaluated sex differences between body composition and laboratory features in relation to femoral neck BMD in RA patients. Approximately 50% of both women and men in our cohort had low femoral neck BMD. ALMI was positively associated with BMD for men and women. High positive anti-CCP carried strong, negative point estimates in the sex-stratified regression models. Although the female subgroup's p-value was on the margin of significance, the independent associations between high positive anti-CCP and femoral neck BMD when stratified by sex failed to reach statistical significance, likely due to lack of power. Additionally, our cohort had sex differences in body composition and physical activity that could contribute to low BMD. A higher percentage of men in this cohort were obese compared to women, and the men demonstrated significant lean mass deficits (17,18). We also noted lower rates of self-reported physical activity among men compared to the

women. RA disease characteristics and current medication use were similar across sexes, however the female participants reported, on average, 4.8 years longer disease duration than males. Therefore, it is possible that there was differential lifetime exposure to glucocorticoids. Glucocorticoids are known to suppress endogenous testosterone production in patients with and without RA (44,45). Testosterone is a key determinant of BMD in men, and low testosterone levels can induce changes in body composition with increased fat and decreased lean mass (46,47). Thus, chronic changes in testosterone could underlie the changes in body composition and femoral neck BMD observed in these men with RA, a hypothesis that would need to be formally tested.

An important limitation of this study is the method by which information on prior osteoporosis medication use was collected, which likely led to incomplete and/or inconsistent reporting by subjects. We were also unable to control for osteoporosis medication use in our cross-sectional model due to the noted inverse association with BMD, which highlights the presence of confounding by indication. To evaluate the effect of osteoporosis medications, we performed a sensitivity analysis removing those who reported osteoporosis medication use, and results were in line with our primary analysis. In addition, the negative linear association increasing of anti-CCP level with BMD was restricted by the upper limit for measurement of anti-CCP level at 250 units, resulting in a clustering of results ≥250 units. However, this constraint should bias our results towards the null hypothesis and decrease our power to detect an effect of anti-CCP level on BMD. Study participants had established RA, which likely increased the prevalence of low BMD and abnormal body composition. Future studies following an incident or early RA cohort would be informative. We were unable to compare demographic or clinical characteristics of study participants and non-participants, so it is possible that this cohort was systematically biased in some way that could impact the results. Our study was cross-sectional, which allowed us to comment only on associations between study variables and BMD and not causation. Additionally, the cross-sectional nature of this study also did not allow us to control for cumulative effects of disease activity and inflammation which are thought to be important contributors to bone loss in RA. We were also unable to account for lifetime glucocorticoid exposure, an important risk factor for altered BMD and body composition. Smoking, a known risk factor for osteoporosis in the general population as well as a contributor to disease activity in RA, had a low prevalence in our cohort and did not show significant associations with BMD, likely due the low number of smokers. We did not obtain 25 hydroxyvitamin D levels in this study, which prevented us from studying the impact of vitamin D deficiency on BMD in these subjects.

In spite of these limitations, the study had several strengths. This study is unique in including measurements of laboratory data, clinical features and functional measures in combination with body composition measures to study BMD. We were able to show that even while controlling for ALMI, an established risk factor for low BMD, as well as for other traditional risk factors for low BMD, high anti-CCP level was an important risk factor for persons with RA. We also had a high percentage of male participants, allowing us to evaluate sex-specific risk factors for low BMD.

Our study has clinical implications for the evaluation and treatment of BMD in patients with RA. As high anti-CCP positivity was associated with lower BMD, such patients may warrant earlier BMD evaluation and treatment. Low ALMI is a modifiable risk factor for low BMD and weight-bearing exercise has been shown to increase BMD both in RA and the general population, so exercise interventions focused on increasing ALMI should encouraged in patients with RA (48). Low muscle mass is also a risk factor for gait instability and fall, which when coupled with low BMD, additionally increases the risk of fracture (39,49), further supporting the importance of exercise to improve muscle mass and gait stability.

In conclusion, we report a strong negative association between high anti-CCP positivity and femoral neck BMD and a strong positive association between ALMI and femoral neck BMD in patients with RA. The association of high anti-CCP positivity with low BMD warrants further study to elucidate the underlying basis of this finding. It may be that ACPAs play a pathogenic role lowering BMD through systemic effects on bone resorption. Alternatively, perhaps the presence of anti-CCP antibodies marks a genetically distinct subset of patients with RA who have other independent risk factors for low BMD. Further studies should be performed to determine if high-positive anti-CCP patients with RA should undergo earlier BMD screening or if efforts should be made to minimize glucocorticoid exposure in this group. Lastly, our study adds to the body of evidence supporting the association of low ALMI with low BMD. As ALMI is a modifiable risk factor for low BMD, research is needed to identify effective means of improving lean muscle mass in RA patients.

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References

1. Haleem S, Lutchman L, Mayahi R, Grice JE, Parker MJ. Mortality following hip fracture: trends and geographical variations over the last 40 years. Injury. 2008; 39:1157–1163. [PubMed: 18653186]
2. Staa TPV, Geusens P, Bijlsma JWJ, Leufkens HGM, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2006; 54:3104–3112. [PubMed: 17009229]
3. Kanis JA, McCloskey EV, Johansson H, Oden A, Ström O, Borgström F. Development and use of FRAX® in osteoporosis. Osteoporos Int. 2010; 21:407–413.
4. Book C, Algulin J, Nilsson JA, Saxne T, Jacobsson L. Bone mineral density in the hand as a predictor for mortality in patients with rheumatoid arthritis. Rheumatology. 2009; 48:1088–1091. [PubMed: 19553375]
5. Lin YC, Li YH, Chang CH, Hu CC, Chen DW, Hsieh PH, et al. Rheumatoid arthritis patients with hip fracture: a nationwide study. Osteoporos Int. 2014; 26:811–817. [PubMed: 25410437]
6. Aizer J, Reed G, Onofrei A, Harrison MJ. Predictors of bone density testing in patients with rheumatoid arthritis. Rheumatol Int. 2008; 29:897–905. [PubMed: 19104820]
7. Solomon DH, Katz JN, Cabral D, Patrick AR, Bukowski JF, Coblyn JS. Osteoporosis management in patients with rheumatoid arthritis: Evidence for improvement. Arthritis & Rheumatism. 2006; 55:873–877. [PubMed: 17139663]

8. Watt J, Thompson A, Le Riche N, Pope J. There is still a care gap in osteoporosis management for patients with rheumatoid arthritis. Joint Bone Spine. 2014; 81:347–351. [PubMed: 24703625]
9. Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. J Rheumatol. 2000; 27:2582–2589. [PubMed: 11093437]
10. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care & Research. 2010; 62:1515–1526. [PubMed: 20662044]
11. Hauser B, Riches PL, Wilson JF, Horne AE, Ralston SH. Prevalence and clinical prediction of osteoporosis in a contemporary cohort of patients with rheumatoid arthritis. Rheumatology. 2014; 53:1759–1766. [PubMed: 24764264]
12. Sambrook PN, Eisman JA, Champion GD, Yeates MG, Pocock NA, Eberl S. Determinants of axial bone loss in rheumatoid arthritis. Arthritis & Rheumatism. 1987; 30:721–728. [PubMed: 3619959]
13. Klop C, de Vries F, Bijlsma JWJ, Leufkens HGM, Welsing PMJ. Predicting the 10-year risk of hip and major osteoporotic fracture in rheumatoid arthritis and in the general population: an independent validation and update of UK FRAX without bone mineral density. Annals of the Rheumatic Diseases. 2016; 75:2095–2100. [PubMed: 26984006]
14. He H, Liu Y, Tian Q, Papasian CJ, Hu T, Deng HW. Relationship of sarcopenia and body composition with osteoporosis. Osteoporos Int. 2015; 27:473–482. [PubMed: 26243357]
15. Ho-Pham LT, Nguyen UDT, Nguyen TV. Association Between Lean Mass, Fat Mass, and Bone Mineral Density: A Meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2014; 99:30–38. [PubMed: 24384013]
16. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Nevill AM, Douglas KM, Jamurtas A, et al. Redefining overweight and obesity in rheumatoid arthritis patients. Annals of the Rheumatic Diseases. 2007; 66:1316–1321. [PubMed: 17289757]
17. Katz PP, Yazdany J, Trupin L, Schmajuk G, Margaretten M, Barton J, et al. Sex differences in assessment of obesity in rheumatoid arthritis. Arthritis Care & Research. 2012; 65:62–70.
18. Baker JF, Long J, Ibrahim S, Leonard MB, Katz P. Are Men at Greater Risk of Lean Mass Deficits in Rheumatoid Arthritis? Arthritis Care & Research. 2014; 67:112–119.
19. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr. 1990; 51:1106–1112. [PubMed: 2349926]
20. Visser M, Pahor M, Tylavsky F, Kritchevsky SB, Cauley JA, Newman AB, et al. One- and two-year change in body composition as measured by DXA in a population-based cohort of older men and women. J Appl Physiol (1985). 2003; 94:2368–2374. [PubMed: 12598481]
21. Knapp KM, Welsman JR, Hopkins SJ, Shallcross A, Fogelman I, Blake GM. Obesity increases precision errors in total body dual-energy x-ray absorptiometry measurements. Journal of Clinical Densitometry. 2015; 18:209–216. [PubMed: 25087044]
22. Giles JT, Ling SM, Ferrucci L, Bartlett SJ, Andersen RE, Towns M, et al. Abnormal body composition phenotypes in older rheumatoid arthritis patients: Association with disease characteristics and pharmacotherapies. Arthritis & Rheumatism. 2008; 59:807–815. [PubMed: 18512711]
23. Giles JT, Bartlett SJ, Andersen R, Thompson R, Fontaine KR, Bathon JM. Association of body fat with C-reactive protein in rheumatoid arthritis. Arthritis & Rheumatism. 2008; 58:2632–2641. [PubMed: 18759279]
24. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr. 2000; 72:694–701. [PubMed: 10966886]
25. Andrews JS, Trupin L, Yelin EH, Hough CL, Covinsky KE, Katz PP. Frailty and reduced physical function go hand in hand in adults with rheumatoid arthritis: a US observational cohort study. Clinical Rheumatology. 2017; 36(5):1031–1039. [PubMed: 28116570]
26. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35:1381–1395. [PubMed: 12900694]

27. Brown WJ, Trost SG, Bauman A, Mummery K, Owen N. Test-retest reliability of four physical activity measures used in population surveys. J Sci Med Sport. 2004; 7:205–215. [PubMed: 15362316]
28. Hagstromer M, Oja P, Sjostrom M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. Public Health Nutr. 2006; 9:755–762. [PubMed: 16925881]
29. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score With 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Cl. Arthritis Care & Research. 2011; 63:S14–S36. [PubMed: 22588741]
30. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism. 2010; 62:2569–2581. [PubMed: 20872595]
31. van der Helm-van Mil AHM, Verpoort KN, Breedveld FC, Toes REM, Huizinga TWJ. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. Arthritis Research & Therapy. 2005; 7:R949–58. [PubMed: 16207336]
32. Bugatti S, Bogliolo L, Vitolo B, Manzo A, Montecucco C, Caporali R. Anti-citrullinated protein antibodies and high levels of rheumatoid factor are associated with systemic bone loss in patients with early untreated rheumatoid arthritis. Arthritis Research & Therapy. 2016; 18(1):226. [PubMed: 27716332]
33. Krishnamurthy A, Joshua V, Haj Hensvold A, Jin T, Sun M, Vivar N, et al. Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated autoantibody-mediated bone loss. Annals of the Rheumatic Diseases. 2016; 75:721–729. [PubMed: 26612338]
34. Harre U, Georgess D, Bang H, Bozec A, Axmann R, Ossipova E, et al. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. J Clin Invest. 2012; 122:1791–1802. [PubMed: 22505457]
35. Orsolini G, Caimmi C, Viapiana O, Idolazzi L, Fracassi E, Gatti D, et al. Titer-Dependent Effect of Anti-Citrullinated Protein Antibodies On Systemic Bone Mass in Rheumatoid Arthritis Patients. Calcified Tissue International. 2017; 101:17–23. [PubMed: 28246933]
36. Shibuya K, Hagino H, Morio Y, Teshima R. Cross-sectional and longitudinal study of osteoporosis in patients with rheumatoid arthritis. Clinical Rheumatology. 2002; 21:150–158. [PubMed: 12086167]
37. Tadashi O, Kentaro I, Masahiro T, Yuko S, Kenji M, Shigeyuki W, et al. Loss of lean body mass affects low bone mineral density in patients with rheumatoid arthritis - results from the TOMORROW study. Modern Rheumatology. 2016; 22:1–20.
38. Şahin G, Guler H, Incel N, Sezgin M, As I. Soft tissue composition, axial bone mineral density, and grip strength in postmenopausal Turkish women with early rheumatoid arthritis: Is lean body mass a predictor of bone mineral density in rheumatoid arthritis? Int J Fertil Womens Med. 2006; 51:70–74. [PubMed: 16881382]
39. Scott D, Seibel M, Cumming R, Naganathan V, Blyth F, Le Couteur DG, et al. Sarcopenic Obesity and Its Temporal Associations With Changes in Bone Mineral Density, Incident Falls, and Fractures in Older Men: The Concord Health and Ageing in Men Project. J Bone Miner Res. 2016; 32:575–583. [PubMed: 27736026]
40. Gnudi S, Sitta E, Fiumi N. Relationship between body composition and bone mineral density in women with and without osteoporosis: relative contribution of lean and fat mass. Journal of Bone and Mineral Metabolism. 2007; 25:326–332. [PubMed: 17704998]
41. Maghraoui El A, Sadni S, Rezqi A, Bezza A, Achemlal L, Mounach A. Does Rheumatoid Cachexia Predispose Patients with Rheumatoid Arthritis to Osteoporosis and Vertebral Fractures? J Rheumatol. 2015; 42:1556–1562. [PubMed: 26233497]
42. Armamento-Villareal R, Aguirre L, Napoli N, Shah K, Hilton T, Sinacore DR, et al. Changes in thigh muscle volume predict bone mineral density response to lifestyle therapy in frail, obese older adults. Osteoporos Int. 2013; 25:551–558. [PubMed: 23892583]

43. Hughes VA, Frontera WR, Dallal GE, Lutz KJ, Fisher EC, Evans WJ. Muscle strength and body composition: associations with bone density in older subjects. Med Sci Sports Exerc. 1995; 27:967–974. [PubMed: 7564983]
44. Martens HF, Sheets PK, Tenover JS, Dugowson CE, Bremner WJ, Starkebaum G. Decreased testosterone levels in men with rheumatoid arthritis: effect of low dose prednisone therapy. J Rheumatol. 1994; 21:1427–1431. [PubMed: 7983641]
45. Reid IR, Ibbertson HK, France JT, Pybus J. Plasma testosterone concentrations in asthmatic men treated with glucocorticoids. British Medical Journal (Clinical research ed). 1985; 291:574–574. [PubMed: 2931151]
46. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, et al. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. Journal of Endocrinological Investigation. 2016; 39:967–981. [PubMed: 27241317]
47. Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol. 2005; 63:280–293.
48. de Jong Z, Munneke M, Lems WF, Zwinderman AH, Kroon HM, Pauwels EKJ, et al. Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: Results of a randomized, controlled trial. Arthritis & Rheumatism. 2004; 50:1066–1076. [PubMed: 15077288]
49. Hars M, Biver E, Chevalley T, Herrmann F, Rizzoli R, Ferrari S, et al. Low Lean Mass Predicts Incident Fractures Independently From FRAX: a Prospective Cohort Study of Recent Retirees. J Bone Miner Res. 2016; 31:2048–2056. [PubMed: 27253633]

Significance and Innovations

- High anti-CCP positivity was associated with lower femoral neck BMD in this group of individuals with RA. Furthermore, in high-positive anti-CCP participants, increasing anti-CCP levels were associated with a negative linear trend in femoral neck BMD.
- Obesity and low lean mass were common in this study, especially in men, which may have contributed to the high rates of low BMD found in both men and women (54% and 51% respectively).
- Greater appendicular lean mass was associated with higher femoral neck BMD. Although this is consistent with previous studies, it suggests an important focus for clinical intervention.

Table 1

Demographic, clinical, body composition, medication and functional variables. Values are presented for the entire cohort (n=138) and by sex.

Variables	Whole cohort (n=138)	Female (n=82)	Male (N=56)	p-value[g]
Basic demographics				
Age	58.0 ± 10.8	58.9 ± 10.6	56.6 ± 11.1	0.231
White Race	107 (78%)	67 (82%)	40 (71%)	0.155
Disease characteristics				
RF Positive	96 (70%)	58 (71%)	38 (68%)	0.719
High Positive Anti-CCP[a]	76 (55%)	41 (51%)	35 (63%)	0.169
Disease duration (years)	19.0 ± 10.9	20.9 ± 11.9	16.1 ± 8.3	0.010
ESR	18.5 ± 18.5	20.0 ± 18.4	16.2 ± 18.7	0.243
CRP	4.7 ± 7.8	4.9 ± 8.7	4.5 ± 6.5	0.761
Current smoker	8 (5.8%)	4 (5%)	4 (7%)	0.576
RADAI Score	2.6 ± 1.8	2.5 ± 1.7	2.7 ± 1.7	0.541
Body Composition				
BMI	27.2 ± 6.0	26.2 ± 5.5	28.6 ± 6.6	0.021
Fat Mass Index	10.8 ± 4.6	10.4 ± 4.2	11.3 ± 5.1	0.252
DXA obese[b]	81 (59%)	36 (44%)	45 (80%)	<0.0001
Appendicular LMI	6.4 ± 1.2	6.1 ± 0.9	6.9 ± 1.4	<0.0001
Femoral neck BMD	0.883 ± 0.137	0.863 ± 0.126	0.911 ± 0.148	0.041
Low BMD[c]	72 (52%)	42 (51%)	30 (54%)	0.786
Medications				
Subjects on prednisone	44 (32%)	26 (32%)	18 (33%)	0.900
Mean dose among those reporting use (mg/day)	7.1 ± 6.1	6.6 ± 4.6	7.9 ± 7.8	0.486
TNF Inhibitor	63 (46%)	32 (39%)	31 (55%)	0.059
Osteoporosis Medication[d,e]	31 (27%)	17 (24%)	14 (31%)	0.371
Calcium[e]	78 (67%)	52 (73%)	26 (58%)	0.084
Vitamin D[e]	87 (75%)	55 (77%)	32 (71%)	0.441
Functional measures				
Low physical activity	46 (33%)	22 (27%)	24 (43%)	0.050
Knee flexion (N-m)[f]	21.6 ± 8.3	21.7 ± 7.5	21.5 ± 9.6	0.920

[a] High positive anti-CCP defined as level >60 units (31).

[b] DXA obese was defined using total percent body fat from DXA based on age, sex, and race-specific criteria (26).

[c] Low BMD was defined as a T-score ≤−1.0 at the femoral neck for those ≥50 years of age and Z-score ≤−1.0 for those <50 years of age.

[d] Osteoporosis medications represent bisphosphonate use. One patient self-reported estrogen use, but was also taking bisphosphonates. No patients recorded use of parathyroid hormone (1–34), raloxifene or calcitonin.

[e] n=117. Due to differences in interview protocols, this question was not asked of all participants.

[f] n=120. Due to patient non-participation in Biodex© measurement.

[g] p-value refers to the difference between female and male study subjects assessed by t-test for continuous variables or χ^2 test for categorical variables.

- RF: rheumatoid factor; CCP: cyclic citrullinated peptide antibody; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; RADAI: rheumatoid arthritis disease activity index, BMI: body mass index; LMI: lean mass index; BMD: bone mineral density; TNF: tumor necrosis factor

Table 2

Univariable linear regressions between variables and femoral neck bone mineral density (g/cm^2) for entire cohort and stratified by sex. Beta coefficients (β) and associated p-values are presented.

	Whole Cohort (N=138)		Female (N=82)		Male (N=56)	
Variables	**β**	**p-value**	**β**	**p-value**	**β**	**p-value**
Basic demographics						
Age	**−0.004**	<0.0001	*−0.002*	0.059	**−0.006**	0.001
White Race	0.000	0.991	0.044	0.221	−0.034	0.444
Male Sex	**0.048**	0.041	n/a	n/a	n/a	n/a
Disease characteristics						
RF Positive	**−0.060**	0.018	**−0.071**	0.020	−0.041	0.334
High Positive Anti-CCP[a]	**−0.069**	0.003	**−0.074**	0.008	*−0.079*	0.052
Disease duration (years)	**−0.003**	0.006	*−0.002*	0.092	*−0.005*	0.061
ESR	0.000	0.749	0.000	0.829	0.001	0.578
CRP	−0.001	0.452	−0.002	0.277	0.001	0.791
Current smoker	0.038	0.447	0.017	0.799	0.051	0.515
RADAI Score	0.006	0.375	*0.014*	0.076	−0.007	0.533
Body Composition Variables						
BMI	**0.006**	0.002	**0.007**	0.006	0.004	0.223
Fat Mass Index	*0.004*	0.083	**0.009**	0.010	−0.001	0.879
DXA obese[b]	0.035	0.143	*0.051*	0.067	0.052	0.298
Appendicular LMI	**0.052**	<0.0001	**0.062**	<0.0001	**0.046**	0.001
Medications						
Prednisone dose	−0.003	0.261	*−0.006*	0.086	−0.001	0.800
TNF Inhibitor	−0.004	0.854	−0.030	0.299	0.013	0.757
Osteoporosis Medication[c,d]	**−0.100**	<0.0001	**−0.079**	0.012	**−0.141**	0.003
Functional measures						
Low physical activity	−0.040	0.106	−0.031	0.334	*−0.073*	0.069
Knee flexion (N-m)[e]	**0.003**	<0.0001	**0.003**	0.035	**0.003**	0.016

Bolded values = significant at p<0.05 level. *Italicized values* = significant at p<0.1 level

[a] High positive anti-CCP defined as level >60 units (31).

[b] DXA obese was defined using total percent body fat from DXA based on age, sex, and race-specific criteria

[c] Osteoporosis medications represent bisphosphonate use. One patient self-reported estrogen use, but was also taking bisphosphonates. No patients recorded use of parathyroid hormone (1–34), raloxifene or calcitonin.

[d] n=117. Due to differences in interview protocols, this question was not asked of all participants.

[e] n=120. Due to patient non-participation in Biodex© measurement.

- RF: rheumatoid factor; CCP: cyclic citrullinated peptide antibody; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; RADAI: rheumatoid arthritis disease activity index, BMI: body mass index; LMI: lean mass index; TNF: tumor necrosis factor

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Table 3

Multivariable linear regression of the entire cohort on the outcome of femoral neck bone mineral density (g/cm^2) (N=117, r^2= 0.353).

Variables	β	95% CI	p-value
Age	−0.003	−0.005 to −0.001	0.009
Male sex	0.014	−0.034 to 0.062	0.567
High Positive Anti-CCP[a]	−0.054	−0.097 to −0.010	0.016
Disease Duration (years)	−0.001	−0.003 to 0.001	0.305
Fat Mass Index	0.001	−0.005 to 0.007	0.723
Appendicular LMI	0.053	0.028 to 0.077	<0.0001
Prednisone dose	0.000	−0.005 to 0.006	0.974
Knee flexion (N-m)	0.002	−0.002 to 0.005	0.328

[a]High positive anti-CCP defined as level >60 units (31).

- CCP: cyclic citrullinated peptide antibody; LMI: lean mass index.

Table 4

Multivariable linear regression on the outcome of femoral neck bone mineral density (g/cm^2) by sex. R^2 for female model 0.279 and for males 0.437.

	Females (N=73)			Males (N=44)		
Variables	**β**	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Age	−0.002	−0.004 to 0.001	0.254	−0.004	−0.008 to −0.001	0.025
High Positive Anti-CCP[a]	−0.055	−0.111 to 0.000	0.051	−0.057	−0.144 to 0.030	0.189
Disease Duration (years)	−0.001	−0.003 to 0.001	0.299	−0.001	−0.007 to 0.005	0.758
Fat Mass Index	0.006	−0.002 to 0.014	0.158	–	–	–
Appendicular LMI	0.037	0.000 to 0.074	0.048	0.060	0.026 to 0.093	0.001
Prednisone dose	−0.003	−0.011 to 0.005	0.470	–	–	–
Knee flexion (N-m)	0.003	−0.002 to 0.007	0.196	0.001	−0.003 to 0.005	0.631

[a]High positive anti-CCP defined as level >60 units (31).

- CCP: cyclic citrullinated peptide antibody; LMI: lean mass index.

- Note: The model for male sex did not include FMI and Prednisone dose due to the small number of male subjects.

Table 5

Multivariable linear regression on the outcome of femoral neck bone mineral density (g/cm^2) for those with high anti-CCP level (>60 units). R^2 for model 0.340. The model did not include FMI and prednisone dose due to smaller sample size (n=61).

Variables	β	95% CI	p-value
Age	−0.003	−0.006 to 0.000	0.083
Male Sex	0.028	−0.037 to 0.094	0.391
Anti-CCP level[a]	−0.011	−0.022 to −0.001	0.026
Disease Duration (years)	−0.002	−0.005 to 0.001	0.138
Appendicular LMI	0.037	0.007 to 0.068	0.018
Knee flexion (N-m)	−0.001	−0.006 to 0.003	0.569

[a]Anti-CCP level per 20 unit increase

- CCP: cyclic citrullinated peptide antibody; LMI: lean mass index.