Effect of Rheumatoid Arthritis on Volumetric Bone Mineral Density and Bone Geometry, Assessed by Peripheral Quantitative Computed Tomography in Postmenopausal Women Treated with Bisphosphonates

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ABSTRACT. ***Objective.*** To investigate the effect of rheumatoid arthritis (RA) on volumetric bone mineral density (vBMD) and bone geometry in postmenopausal women treated with bisphosphonates.

Methods. Fifty-three postmenopausal women with RA and 87 control subjects, comparable in terms of age, body mass index, and years since menopause, underwent peripheral quantitative computed tomography (pQCT) of the nondominant tibia.

Results. At 4% (trabecular site), trabecular bone mineral content (BMC) and vBMD ($p < 0.001$) were lower in the RA group, while trabecular area was comparable. At 38% (cortical site), cortical BMC ($p < 0.01$), area ($p < 0.05$), and thickness ($p < 0.001$) were lower in the RA group, whereas vBMD was comparable. Endosteal circumference was higher ($p < 0.05$), whereas periosteal circumference was comparable, indicating cancellization of cortical bone. In the RA group, muscle area was lower ($p < 0.001$), while at 14% polar stress strength index was significantly lower ($p < 0.01$) in patients with RA, indicating impairment of bone mechanical properties.

Conclusion. RA is associated with negative effects on both cortical and cancellous bone in postmenopausal women treated with bisphosphonates. Cortical geometric properties are also adversely affected mainly by increased endosteal circumference, whereas trabecular geometric properties are generally preserved. (First Release April 1 2012; J Rheumatol 2012;39:1215–20; doi:10.3899/jrheum.110579)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is an autoimmune disease affecting 0.5% of the general population, with increased prevalence in females and with older age[1,2,3,4]. Periarticular bone loss, bone erosions, and systemic osteoporosis represent the cardinal musculoskeletal features, attributed to the inflammatory nature of the disease, reduced mobility, and longterm treatment with corticosteroids[1,5,6,7,8]. The frequency of osteoporosis in postmenopausal women with RA is up to 30% depending on the site tested[1,9], at least double the reference population, with preferential bone loss at the appendicular skeleton, albeit with large interindividual variations. Risk factors for bone mineral density (BMD) reduction in RA include older age, low body weight, corticosteroid use, rheumatoid factor positivity, and high disability scores. Moreover, the risk of low-trauma or spontaneous fractures is doubled in patients with RA, especially at the hip, spine, pelvis, humerus, and tibia[1,10], with the risk remaining elevated independent of BMD and corticosteroid use[11]. Indeed, RA is the only secondary cause of osteoporosis that is considered independent of bone density in the World Health Organization fracture risk assessment tool algorithm[12].

Common skeletal sites for assessment of bone involvement in patients with RA include the hand, using digital radiogrammetry (DXR) and dual-energy x-ray absorptiometry (DEXA), a fast, noninvasive, and cost-effective technique for measuring areal bone mineral density (aBMD). Other sites are the lumbar spine and hip, using DEXA.

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Although hand assessment is more specific for RA, occurs early in the course of the disease, and is associated with systemic bone loss[13,14], data linking hand bone loss with fragility fractures are scarce[15], while bisphosphonates (BP), commonly used for the prevention and treatment of glucocorticoid-induced osteoporosis in RA, do not affect hand bone loss. Moreover, bone strength also depends on the geometrical properties of its structure, information that cannot be derived from planar DEXA images. However, peripheral quantitative computed tomography (pQCT) allows separate measurements of the true volumetric bone density (mg/cm^3) and cross-sectional areas of trabecular and cortical bone, thus providing additional information regarding bone geometry[16,17]. PQCT also combines a series of advantages regarding both its infrastructure, which is more portable and less costly compared to DEXA and QCT equipment, and its routine clinical use, since it requires lower radiation dosage in contrast to other techniques[18]. Measurement sites include the radius and the tibia. The tibia is subject mainly to compressive force at distal sites and bending forces at the diaphysis, while the radius is subject mainly to bending and torsional forces[19]. Most importantly, evidence has established the prognostic significance of pQCT-derived measures regarding fracture risk[20,21].

The effects of RA at the radius[22,23,24,25] and tibia[26,27] have been analyzed in studies mostly involving children and adolescents with juvenile idiopathic arthritis (JIA). The only study that used pQCT at the radius, tibia, and third metacarpal bone in women with RA[28] reported significant reduction of trabecular BMD at the radius and tibia and reduced cortical BMD and thickness at the radius, while at the tibia only cortical thickness was reduced. However, that study included both premenopausal and postmenopausal women, while 72% were taking glucocorticoid therapy and 35% were receiving BP. Because most postmenopausal women with RA treated with corticosteroids should probably receive BP for the prevention of glucocorticoid-induced osteoporosis[29], information about the effect of BP on volumetric BMD (vBMD) and bone geometry is of substantial clinical importance. Thus our study adds new data on both quantitative and qualitative bone characteristics using pQCT at the nondominant tibia, a site subject to different mechanical loading compared to the radius, in postmenopausal women with RA treated with corticosteroids and BP.

MATERIALS AND METHODS

From February 2007 to November 2008, 65 postmenopausal women with RA were recruited for our study. They fulfilled the American College of Rheumatology[4] criteria for RA, and were aged 46 to 75 years. Twelve patients were excluded because of secondary causes of osteoporosis (2 primary hyperparathyroidism, 4 low concentration of 25(OH) D < 20 ng/ml, 3 hyperthyroidism, 2 renal disease, and 1 severe hepatic disease), leaving 53 for final evaluation. All patients were receiving calcium and vitamin D supplements; all but 2 were also treated with oral BP as prophylaxis for corticosteroid-induced osteoporosis. Disease activity and progression were estimated using the 28-joint Disease Activity Score (DAS28).

Controls were white postmenopausal women evaluated in our department for osteoporosis, matched with patients with RA for age, years after menopause, and body mass index (BMI). All subjects had normal plasma parathyroid hormone and calcium concentrations, 25(OH)D levels > 20 ng/ml, and no identifiable cause of secondary osteoporosis. The protocol was designed according to the Declaration of Helsinki and approved by the Ethics Committee of KAT Hospital. All subjects gave written informed consent.

VBMD and geometric properties estimation by pQCT. PQCT bone mineral measurements and analyses were performed at the nondominant tibia, using the XCT-3000 device (Stratec GmbH, Pforzheim, Germany)[30,31]. A single-energy radiography source was used. All CT scans had a slice thickness of 2.4 mm and a voxel size of 0.5 mm^3. The distal end of the tibia was used as an anatomical marker; the bone cross-sectional area was imaged at slices 4%, 14%, 38%, and 66% of the tibia length, proximal to this point. In analyzing each slice, the vBMD, corresponding bone mineral content (BMC), and cross-sectional area (CSA) of tibia bone section were estimated, as well as cortical thickness, endosteal and periosteal circumference, and polar stress strength index in torsion (SSIp). Image analysis was performed using integrated software (Stratec XCT-3000, version 5.4).

Total trabecular and cortical bone density (from the periosteum, including area of the bone and bone marrow) in mg/cm^3 and the CSA of the corresponding bone portions in mm^2 were calculated by the following procedure: (1) voxels outside the bone (soft tissue) with lower attenuation coefficients than the selected threshold (181 mg/cm^3) were removed within the region of interest; and (2) the cortical and trabecular structures were separated by the areal distribution of both bone structures. By default, 55% of the outer bone area was concentrically separated and defined as the cortical-subcortical region. The remaining 45% of the inner core was defined as trabecular bone. Therefore, bone marrow is included in the estimation of total and trabecular area but eliminated in the estimation of the respective BMC. To calculate pure cortical density and area without including the subcortical area, all voxels within the region of interest that have an attenuation coefficient below the threshold 710 mg/cm^3 density were removed.

Cortical thickness was defined as the mean distance between inner and outer edge of the cortical shell. SSIp lies within the theory of stability of mechanical structures against bending or torsion. From CT cross-sectional images, the determination of bone strength is based on the calculation of the cross-sectional moment of inertia (CSMI). CSMI was calculated as

$$\sum (V_i - C_i)^2 \times \text{voxel area}$$

where V_i was the position of the voxel i, C_i was the position of the center voxel (the centric voxel of the identified bone), and $\sum$ was the sum taken for all voxels inside the measurement contour of cortical CSA. Division of cross-sectional moment of inertia by the maximum distance of any voxel from the center of gravity (r_{max}) yields the section modulus that is directly proportional to maximum stress in bone. To take the material properties into consideration, the section modulus is multiplied by the quotient of calculated cortical density and normal physiological cortical density of 1200 mg/cm^3, yielding the calculation of SSIp. At the 66% slice, muscle CSA was calculated. The longterm *in vitro* (phantom) precision of the pQCT in 12-month daily measurements was 0.12% for total vBMD and 0.3% for trabecular vBMD. The *in vivo* precision, derived from 25 postmenopausal women subjected to duplicate measurements within 1 month, was as follows (mean ± SD): total vBMD, 0.2 ± 0.13; trabecular vBMD, 0.46 ± 0.26; cortical area, 0.34 ± 0.19; SSIp, 1.02 ± 0.63; and cortical thickness, 0.83 ± 0.48.

Statistical analysis. Normality was tested using the Kolmogorov-Smirnov test. Accordingly, data are presented as mean ± SD or median (minimum-maximum) in case of non-normally distributed variables. Between-group differences were analyzed by unpaired t tests. Analysis of covariance was used to estimate the differences in vBMD and geometric measures independent of differences in muscle area between patients and controls. Bivariate correlations were estimated by Spearman test. Statistical significance was set at $p < 0.05$. All data analysis was performed using the Statistical Package for Social Sciences (version 13.0) software (SPSS Inc., Chicago, IL, USA).

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RESULTS

Baseline characteristics. Baseline characteristics are presented in Table 1. The 2 groups were comparable in terms of age, weight, height, BMI, and years since menopause. Mean duration of the disease was 9.4 years and the average DAS28 score was 3.75 ± 1.47. All patients were treated with corticosteroids at an average daily dose of 6.6 ± 1.9 mg. Median cumulative dose was 8212 mg (range 54–73,000). A majority of our patients (81%; 43/53) was also treated with methotrexate (MTX), while the rest (19%; 10/53) were receiving leflunomide.

Comparison of vBMD and bone geometry between groups by pQCT. On the trabecular site (4% of tibia length, Table 2), total vBMD (12.5%) and total BMC (11.6%; data not shown) as well as trabecular BMC (14.7%) and vBMD (15.6%) were significantly lower in patients with RA compared with controls (all $p < 0.001$). Total CSA and trabecular CSA were comparable between groups ($p > 0.05$). Adjustment for muscle area did not alter the results.

On the cortical site (38% of tibia length), total vBMD (5.1%; $p = 0.001$) and total BMC (5.9%; $p < 0.01$; data not shown) as well as cortical BMC (7.35%; $p < 0.01$) were significantly lower in patients with RA. Cortical vBMD tended to be lower in patients with RA, although not significantly, compared with controls ($p = 0.066$). Cortical CSA was significantly lower (6.52%; $p < 0.05$) in patients with RA compared with controls. Further, endosteal circumference was higher (4.46%; $p = 0.046$), whereas cortical thickness was lower (7.7%; $p = 0.001$) compared with controls. In addition, periosteal circumference was comparable between the 2 groups ($p = 0.583$). Adjustment for muscle area did not particularly alter the results.

Finally, muscle area, assessed at 66% of tibia length, was significantly lower in patients with RA (10.4%; $p < 0.001$).

In the transition zone (14% of tibia length), both trabecular and cortical BMC were significantly lower (26.17% and 11.6%, respectively; all $p = 0.001$) in patients with RA compared with controls, while the corresponding vBMD was reduced only concerning cortical bone (3.9%; $p = 0.001$). Total CSA and trabecular CSA were comparable between groups ($p > 0.05$), whereas cortical area was reduced in the RA group (8.4%; $p = 0.001$). SSIp was lower in patients with RA compared with controls (8.6%; $p = 0.007$). Adjustment for muscle area removed the observed difference.

Correlation analysis. Correlation analysis of various disease measures with vBMD and bone geometric indices in patients with RA revealed modest positive association of age with endosteal circumference ($r = 0.296$, $p = 0.031$) and negative with cortical vBMD ($r = –0.407$, $p = 0.003$). Cumulative steroid dose showed modest negative association with cortical area ($r = –0.291$, $p = 0.034$). Correlation analysis of BMI, C-reactive protein, DAS28 score, and disease duration did not reveal any particular association. Muscle area had significant positive association with trabecular BMC ($r = 0.325$, $p = 0.019$), cortical area ($r = 0.506$, $p < 0.001$), cortical thickness ($r = 0.401$, $p = 0.003$), periosteal circumference ($r = 0.427$, $p = 0.002$), and most importantly, SSIp ($r = 0.578$, $p < 0.001$).

Table 1. Baseline characteristics of the 2 study groups. Data are mean ± SD, except where indicated.

Characteristics	RA Group, n = 53	Control, n = 86	p
Age, yrs	61.71 ± 9.28	60.13 ± 7.86	0.15
Weight, kg	67.18 ± 10.19	66.91 ± 7.88	0.85
Height, cm	156.71 ± 6.24	158.01 ± 3.53	0.12
Body mass index, kg/m^2	27.49 ± 4.82	26.79 ± 4.44	0.41
Years since menopause	13.23 ± 7.97	11.72 ± 8.39	0.29
Disease duration, yrs	9.4 ± 7.5	NA	—
Functional stage	II–III	NA	—
DAS28	3.75 ± 1.47	NA	—
CRP, mg/dl, range	0.4 (0.09–7.3)	NA	—
Daily prednisone dose, mg	6.6 ± 1.9	NA	—
Cumulative prednisone dose, mg	8212 (54–73000)	NA	—
DMARD, n (%)		NA	—
Methotrexate	43 (81)	—	—
Leflunomide	10 (19)	—	—
Calcium and vitamin D	53 (100)	83 (95.4)	—
Bisphosphonates	51 (96.2)	—	—

RA: rheumatoid arthritis; NA: not applicable; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drugs.

DISCUSSION

Our study was designed to investigate the effect of RA on vBMD and bone geometry using pQCT, at a weight-bearing bone such as the tibia in postmenopausal women treated with corticosteroids and BP. Our main findings, regarding trabecular bone, suggest that RA leads to a significant loss of BMC, indicative of demineralization of cancellous bone. Concerning cortical bone, bone density was not significantly decreased in the RA population compared with controls, due to the concomitant decrease of both BMC and area. Moreover, major changes were noted in terms of bone geometry. Specifically, patients with RA presented significant loss of cortical thickness, probably due to increased endocortical resorption, because endosteal circumference was increased while periosteal circumference was comparable. Indices of disease activity were not related with bone measurements, apart from a modest association of cumulative corticosteroid dose with demineralization of trabecular bone. Finally, muscle mass was markedly reduced in patients with RA and showed significant association with vBMD and geometric properties. However, most bone "deficits" in patients with RA remained significant after adjustment for muscle area, indicating that apart from muscle atrophy, other disease-related processes contribute to impairment of bone strength.

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Table 2. Volumetric bone mineral density (vBMD), bone mineral content (BMC), and bone geometric characteristics assessed by peripheral quantitative computed tomography. Data are mean ± SD.

Measure	RA Group	Control Group	p	p*
4% site (trabecular)				
BMC, mg	83.80 ± 20.01	98.3 ± 14.56	0.001	0.001
vBMD, mg/cm^3	175.84 ± 40.77	208.37 ± 26.59	0.001	0.001
CSA, mm^2	479.38 ± 59.22	474.45 ± 58.56	0.632	0.292
38% site				
Cortical BMC, mg	249.46 ± 42.15	269.27 ± 30.75	0.002	0.026
Cortical vBMD, mg/cm^3	1113.83 ± 39.59	1125.39 ± 33.55	0.066	0.039
Cortical CSA, mm^2	223.66 ± 36.03	239.28 ± 26.36	0.004	0.090
CRTHK, mm	4.099 ± 0.66	4.444 ± 0.48	0.001	0.009
PERI, mm	67.61 ± 3.47	67.99 ± 4.25	0.583	0.760
ENDO, mm	41.859 ± 4.60	40.068 ± 5.40	0.046	0.035
14% site				
Total BMC, mg	193.62 ± 35.10	218.35 ± 21.38	0.001	0.017
Total vBMD, mg/cm^3	407.155 ± 83.24	468.25 ± 70.89	0.001	0.01
Total CSA, mm^2	483.03 ± 69.54	475.6 ± 78.12	0.57	0.44
Trabecular BMC, mg	19.38 ± 10.30	26.25 ± 8.83	0.001	0.004
Trabecular vBMD, mg/cm^3	91.07 ± 48.73	125.96 ± 47.83	0.001	0.005
Tabecular CSA, mm^2	217.25 ± 31.29	213.9 ± 35.16	0.57	0.44
Cortical BMC, mg	149.74 ± 30.80	169.50 ± 20.32	0.001	0.004
Cortical vBMD, mg/cm^3	931.16 ± 73.74	968.96 ± 53.29	0.001	0.007
Cortical CSA, mm^2	159.96 ± 26.6	174.75 ± 16.97	0.001	0.003
SSIp, mm^3	1147.32 ± 235.89	1256.41 ± 221.7	0.007	0.123
66% site				
Muscle area, mm^2	5263.77 ± 957.65	5851.59 ± 772.67	0.001	NA

* Analysis of covariance, adjusted for muscle area. CSA: cross-sectional area; CRTHK: cortical thickness; PERI: periosteal circumference; ENDO: endocortical circumference; SSIp: polar stress strength index; NA: not applicable.

Previous DEXA studies have shown a marked decrease of BMD especially at the hip[1,6,9,32] and radius[33] in patients with RA. Data regarding volumetric BMD and bone geometry in patients with RA are scarce, refer mainly to children and adolescents, and reach mixed results possibly because of the heterogeneity of the disease and the effect of disease-modifying agents. In general, our results are in accord with a study by Aeberli, *et al*[28] that has shown a profound reduction of trabecular BMD, cortical thickness, and muscle area of the tibia in patients with RA compared to healthy controls. Aeberli, *et al* also reported significant association of erosive status and muscle mass with pQCT indices, while no association was observed with steroid treatment. Martin, *et al*[34], in a study of postmenopausal women with RA and using pQCT at the radius, reported significant reduction of trabecular vBMD and femoral neck aBMD, no differences in radial cortical vBMD and spine aBMD between patients and controls, and significant association of BMD loss with disease activity. No differences were observed between steroid-naive and steroid-treated patients. Felin, *et al*[27] reported marked reduction of trabecular BMD at the site of the distal tibia in patients with juvenile rheumatoid arthritis. Similar to our results, cortical vBMD was not affected, while muscle mass was reduced and bone geometry was impaired by cortical thinning. The Felin study found that steroid treatment and disease activity were associated with more severe bone abnormalities[27]. Similar results were reported by Burnham, *et al*[26] at the tibia in a heterogeneous group of patients with JIA. On the other hand, a pQCT study performed at the radius by Shibuya, *et al*[25], has shown that total BMD, trabecular vBMD, and cortical vBMD were reduced early after onset of RA and did not alter significantly during the course of the disease. Enokida, *et al*[35] also conducted a pQCT study examining the effect of collagen-induced arthritis (an experimental model for RA) on bone mass of young and old rats. They concluded that the decrease in cortical BMD was delayed compared to trabecular BMD.

We should point out that our patients were already under treatment for RA with glucocorticoids and disease-modifying antirheumatic drugs (DMARD) at the time of recruitment. The influence of corticosteroids on bone, among patients with RA, has been evaluated in previous studies[1]. Indeed, in patients with RA receiving glucocorticoids, there is a higher prevalence of vertebral deformities and symptomatic vertebral fractures as compared to those without steroids[36]. However, the effect of glucocorticoids on bone in RA must be considered also in terms of their antiinflammatory actions. Gough, *et al* demonstrated an accelerated BMD loss in patients with early RA in comparison to controls at the spine and trochanter[37]. In that study, the greatest bone loss was observed with low steroids — already toxic for

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bone formation but inefficient to suppress disease activity. Thus it is possible that control of inflammation by steroids might counterbalance to a point the adverse bone effects[1,38,39,40].

Nevertheless, the majority (96%) of our study population was also receiving BP as part of the prophylaxis of glucocorticoid-induced osteoporosis along with calcium and vitamin D. In general, BP suppress bone remodeling, the effect being most prominent at trabecular sites and less prominent at cortical sites such as the femur and the tibia[41]. Data concerning the effects of BP on bone geometric properties are limited, with most data coming from large randomized controlled trials using QCT[42,43,44,45]. In some of these studies, BP increase trabecular vBMD at the spine and hip, while in some there was also an increase in either cortical bone volume and compression strength index at the hip[42] or cortical femoral neck vBMD[44]. Conversely, a study using pQCT at the tibia in women with postmenopausal osteoporosis[46] and evaluating the additive effects of alfacalcidol over standard treatment with alendronate reported stability or even borderline decline in some pQCT measures. Thus it is possible, given the limitations of our cross-sectional design, that BP only attenuate the impairment in bone biomechanical properties in patients with RA who are treated with steroids.

Lastly, the effect of DMARD on bone should also be considered. In our population, 43 patients were treated with MTX and 10 with leflunomide. The effect of MTX on bone remains controversial. Experimental studies suggest that MTX inhibits osteoblast differentiation[47] and enhances osteoclastic activity[48]. High doses of MTX have been associated with severe osteopathy in children with leukemia[49]. However, low-dose regimens such as those used in the treatment of RA appear to have no negative effect on cortical or trabecular BMD[50]. The effect of leflunomide on bone remains unclear; in the only study available at present, leflunomide appears to slightly increase periarticular BMD at the site of the metacarpals as measured by DXR[51].

There are limitations to our study. First, the number of patients with RA was relatively small. A second limitation applies to the cross-sectional design. Moreover, almost all patients were receiving BP as part of osteoporosis prophylaxis. Thus one can speculate that our results might underestimate the adverse effects of inflammation or steroid treatment on volumetric BMD and bone geometry. Finally, our results concern only postmenopausal women with RA, and conclusions should not be extrapolated for populations with different characteristics such as premenopausal women or men with RA.

RA is associated with negative effects at both cortical and cancellous bone in postmenopausal women even under treatment with BP. Cortical geometric properties are also adversely affected, mainly by increased endosteal circumference, whereas trabecular properties are generally preserved.

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